

# A TEXT-BOOK OF PATHOLOGY

*An Introduction to Medicine*

ACC. 29386  
31/12/02

BY

**WILLIAM BOYD**

M.D., Dipl. Psych., M.R.C.P. (Edin.), F.R.C.P. (Lond.), F.R.C.S. (C),  
LL.D. (Sask.), D.Sc. (Man.), M.D. (Oslo), F.R.S. (C)

*Professor of Pathology, University of British Columbia, Vancouver, B. C. Canada,*

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1953

*First Edition, 1932*

Reprinted, 1933

*Second Edition, 1934*

Reprinted, 1934

Reprinted, 1935

Reprinted, 1935

Reprinted, 1936

*Third Edition, 1938*

Reprinted, 1938

Reprinted, 1939

Reprinted, 1940

Reprinted, 1941

*Fourth Edition, 1943*

Reprinted, 1943

Reprinted, 1944

Reprinted, 1944

Reprinted, 1945

Reprinted, 1946

*Fifth Edition, 1947*

Reprinted, 1947

Reprinted, 1948

Reprinted, 1948

Reprinted, 1949

Reprinted, 1950

Reprinted, 1951

Reprinted, 1952

*Sixth Edition, 1953*

Reprinted, 1954

First Spanish Edition, 1952

First Portuguese Edition, 1946

Second Portuguese Edition, 1949

Library of Congress Catalog Card Number: 53-9568

Printed in the United States of America

## PREFACE TO THE SIXTH EDITION

THE task of revising a book on a medical subject is not an easy one at the present time. Advances in knowledge are so rapid that an author is overwhelmed by the amount of new material with which he is confronted. The temptation is simply to add what is new. There comes a time, however, when, instead of merely adding more and more material, the task must be faced of digesting and assimilating the new matter with the mass of pre-existing knowledge. In some ways it is easier to write a new book, for the danger of pouring new wine into old bottles is well recognized.

Never before has the constantly changing character of the picture of disease become so apparent. Diseases which formerly were common and fatal have disappeared or have become comparatively trivial owing to improved preventive measures, to chemotherapy and to the use of antibiotics. Diphtheria and typhoid fever, syphilis and puerperal fever, acute osteomyelitis and a host of other conditions come to mind. In these and other instances the belt of speech has had to be tightened, just as dead wood must be pruned, leaving room for the young shoots.

Unfortunately new lesions and new diseases have appeared in the wake of the great wave of successful therapy. Viral pneumonias have replaced the bacterial forms, the lesions of healed periarteritis nodosa and tuberculous meningitis are not without danger, and the wholesale change in the normal bacterial flora of the bowel produced by antibiotics may have dangerous or even fatal consequences. In 1951 over 73,000,000 pounds of synthetic chemicals were administered with or without good reason in the United States, or half a pound for every man, woman and child in the country. Chemotherapy and hormonotherapy are only superficially an unalloyed blessing, for while solving some problems they help to create new ones. It must not be forgotten that what is powerful for good can also be potent for evil, and, as Friar Laurence remarks in *Romeo and Juliet*, "virtue itself turns vice, being misapplied."

It may assist the reader to list the new material, even though in some cases the account has necessarily had to be brief. The new subjects are as follows: The miscible pool of uric acid in gout, amniotic fluid and atheromatous embolism, tuberculoid lesions, asteroid inclusions, the influence of cortisone on inflammation and healing, the concept of field of influence in relation to repair, cat scratch disease, salivary gland inclusion disease, epidemic hemorrhagic fever, rickettsial pox, exfoliative cytology, thrombotic non-bacterial endocarditis, traumatic injury of the heart, deficiency myocarditis, the Eisenmenger complex, sarcoidosis of the myocardium, coronary artery calcification in infancy, endocardial fibroelastosis, diffuse collagen disease, thrombophlebitis migrans, malignant granuloma of nose, bronchiolitis fibrosa obliterans, pneumoconiosis due to beryllium, bauxite and graphite, intralobar sequestration of the lung, pulmonary moniliasis, coccidioidomycosis and histoplasmosis, idiopathic pulmonary fibrosis,

pulmonary adenomatosis and hamartoma, the broncho-pulmonary venous circulation in emphysema, mediastinal tumors and cysts, tumor of the glomus jugularis, tumors and cysts of the jaws, antibiotic enteritis, intestinal pneumatosis, canicola fever, extrapancreatic lesions of diabetes, the Ellis concept of glomerulonephritis, vacuolar nephropathy, papillitis necroticans. Reiter's syndrome, infarct of the prostate, Berger's tumor of the ovary, plasma cell mastitis, pathological physiology of the adrenal, stress, primary reticuloendothelial granulomas, Letterer-Siwe disease, myeloid metaplasia of the spleen, lipomelanotic reticular hyperplasia, hypersplenism, thrombotic thrombocytopenic purpura, occlusion of the internal carotid artery, incisural sclerosis in epilepsy, drug encephalitis, cerebral toxoplasmosis, Cocksackie virus disease, Alzheimer's disease, classification of the gliomas, Guillain-Barré syndrome, acute porphyria, osteoid osteoma, villo-nodular synovitis, Marfan's syndrome, dermatomyositis, the anterior tibial syndrome, diseases of the skin, and, in relation to dental pathology, gingivitis, osteomyelitis of the jaw, maxillary sinusitis, and deep neck infections.

Sections which have been rewritten in part or in whole include the following: Gangrene, mechanism of thrombosis, syphilis, schistosomiasis, the general pathology of tumors including pathogenesis, the radiosensitivity of tumors, the spread of tumors, auricular and ventricular septal defects, disseminated lupus erythematosus, the etiology and pathogenesis of atheroma, the histology of emphysema, bronchogenic carcinoma, hepatic necrosis, ulcerative colitis, glomerulonephritis, nephrosis, the renal lesions in eclampsia, intercapillary glomerulosclerosis, thyroiditis, the nature of pernicious anemia, the hemolytic anemias, hepato-lenticular degeneration, and the etiology of rheumatoid arthritis.

Diseases of the skin form so large and specialized a subject that I have hesitated in the past to include a section dealing with this branch of pathology. Dermatopathology, however, has developed so greatly and the practice of making skin biopsies has grown to such an extent that a final chapter has been added dealing with some skin disorders. In this chapter the section on nevi and the melanomas has been included and rewritten.

The contentious matter of small type is always a difficult one to decide. Theoretically such type should be reserved for what is unimportant and rare. The difficulty is to decide what is unimportant. What is rare in one part of the world may be common in another. For better or worse, a good deal of what was previously in large type has been changed to small, chiefly with the object of making room for new material. In the main, general principles are given in large type, whilst minutiae and rarities are relegated to small type. There are seventy more figures and three new color plates. The book is reduced in size by thirty pages.

Much of the stimulus and many of the ideas for this revision I owe to my associates, Dr. H. J. Barrie of the University of Toronto, and Dr. H. K. Fidler and Dr. H. E. Taylor of the Vancouver General Hospital. My former pupil, Dr. Fidler, has helped greatly to simplify the complexities of skin pathology. Dr. Taylor has taken the photographs illustrating the chapter on the skin: the quality of these pictures may appeal to those who

appreciate such matters. Dr. David Zack has given me valuable advice in the revision of the chapter on dental pathology. I am particularly indebted to Dr. Clarisse Aszkanazy and Dr. Hugh A. MacMillan for correction of the proofs and to Dr. C. J. Coady for the preparation of the index.

Finally I have much pleasure in taking this opportunity of expressing to my publishers my appreciation of the long-suffering and patience they have shown in granting my frequent requests for permission to insert new material in the proofs up to the last minute so that the book might be as up-to-date as possible.

WILLIAM BOYD

VANCOUVER, B. C.

## PREFACE TO THE FIRST EDITION

A SPEAKER, whatever his subject, must keep his audience in mind, otherwise he is lost. Nor can the writer afford to forget this elementary truth. He also has his audience, and different classes of audience demand different treatment. It is customary to describe a book as intended for students and practitioners, but the more satisfactory it is for the one type, the less satisfactory is it apt to be for the other. The practitioner may at any time meet the rarest and most obscure of diseases. He will therefore wish to have a book to which he can refer; it must be a book of reference. The object of the student, on the other hand, should be to gain a grasp of the fundamental principles underlying the subject. These he must learn and digest. The time at his disposal is so limited that he cannot afford to dissipate it on intriguing rarities or the newest notion of the moment, else he will find that he will know less and less about more and more; he will be "ever learning and never able to come to the knowledge of the truth." Too often he is sacrificed to satisfy the author's sense of completeness. There must, then, be books for reference and there must be books for reading. The present volume does not belong to the former class. It is intended for the student of pathology, whether undergraduate or postgraduate, not for the practitioner in that subject, *i. e.*, the pathologist and professional laboratory worker. For the latter there are already a number of excellent texts both English and German, as well as the monumental system of Henke and Lubarsch in fourteen volumes.

General pathology is the elucidation of the vital processes which underlie the end-results studied by the morbid anatomist. It is the study of disease from the physiological point of view. The study of special pathology should be pursued in a similar manner. Pathology, if it is to remain alive, must become physiological in its outlook. For this reason the section on the female reproductive system opens with a discussion of the physiology of menstruation, the section on bones with the physiology of bone, the section on the ductless glands with the physiology of those organs, and so on. It is easy to point out that a certain type of uterine hemorrhage is constantly associated with hypertrophy of the endometrium characterized by certain histological changes which used to be known as glandular endometritis. But when we discover that both the hemorrhage and the structural changes in the uterus have a common origin in disturbance of ovarian function the entire subject of the pathology of the endometrium acquires a different meaning. Unfortunately the physiological outlook is not always possible, and the pathologist may have to content himself with applying a great variety of names to an equally great number of states, the relationship and meaning of which he really does not understand. The student must learn to recognize that ignorance, however aptly veiled in an attractive terminology, still remains ignorance.

Physiology cannot be allowed to remain in its own watertight compartment. It must come out and contribute to the subject of pathological physiology. In the same way pathology must not confine itself to a study of states, but must include a consideration of disordered processes. As Sir Michael Foster once remarked with characteristic penetration: "The science of meteorology cannot be divided into the science of good weather and the science of bad weather." The study of morphology and pathological physiology, of altered structure and disordered function, must go hand in hand, greatly to the mutual benefit of both. A world of disordered function lies revealed in any lesion if we only have the eye to see it. A healed tuberculous scar in the lung should conjure up a sharp attack, a stubborn defense, temporary defeat, but ultimate victory.

It has become the fashion to regard morbid anatomy, both gross and microscopic, as somewhat of an outworn creed, a science as dead as the material with which it deals. But morbid anatomy is not dead and never has been, except in the hands of those whose dull minds would take the breath of life from the most vital subject. When taught by the masters of the past, morbid anatomy, so far from being dead, has been the living framework of a living body. The world of medicine did not think that there was anything dead about the "Cellular Pathologie" when Virchow poured the new wine of his vital spirit into the old bottles of tradition. And the bottles are not yet full.

There is much talk in the present day regarding the coördination of the various subjects of the medical curriculum. The study of pathology in the proper spirit is the best means of breaking down the partitions which separate the subjects, for such a study forms a common meeting-ground for anatomy, histology, physiology, biochemistry and clinical medicine. Pathology is not a pure science. The pathological changes are merely one side of a problem, of which the other side is furnished by the clinical picture. Each throws light upon the other and neither is complete by itself. One of the most significant of the early symptoms of cancer of the stomach is anorexia, a distaste for food. A healthy appetite is dependent on the muscle tone of the stomach wall, and this tone is destroyed by the infiltration of carcinoma cells between the muscle fibers which forms so characteristic a feature of the microscopic picture. When this is realized, both the anorexia and the histological appearance will acquire a richer significance and a fuller meaning. To these statements an exception must be made in favor of general pathology, which may be studied in much the same way as a pure science is approached.

Pathology in relation to the living patient is the motif of this book. It is intended to serve as an introduction to medicine and surgery. The medical student who steps from the laboratory into the clinical years is apt to find himself in a very unfamiliar country where for a time he may be lost to a degree little guessed by his clinical teachers. In many schools the study of pathology is commenced at the same time as the study of medicine, surgery and gynecology. The student knows nothing about the symptoms caused by the pathological lesions he sees, so that he is unfitted to attempt that correlation of clinical symptoms with pathological lesions which forms one of the most valuable exercises in a course of morbid anatomy. With the

idea of overcoming this difficulty the account of all the more important diseases is preceded by a brief summary of the clinical symptoms. Then comes the usual description of the morbid anatomy, and this is followed by an attempt to correlate the symptoms with the lesions. It is hardly necessary to defend the introduction of a brief account of symptoms, for the text-books of medicine and surgery do not hesitate to preface the discussion of clinical manifestations by a survey of the morbid anatomy which frequently does not err on the side of brevity. For these reasons I have ventured to use the sub-title: "An Introduction to Medicine."

To the student the value of a persistent endeavor to correlate symptoms with lesions lies not so much in the number of facts which he may succeed in memorizing, as in the development of an attitude of mind which may color the whole of his future professional career. The clinical-pathological conference owes its popularity to the realization of this fact. Education can achieve no higher success than by leaving its abiding imprint on the mental outlook of those who come under its influence.

To the clinician who wishes to indulge in the periodic brain-dusting recommended by Osler there are few more valuable correctives than a renewed acquaintance with the facts of morbid anatomy as revealed in the postmortem room. It is more than one hundred and thirty years since Bichat wrote the following words, but they are as true today as they were then: "You may take notes for twenty years from morning to night at the bedside of the sick upon the diseases of the heart, the lungs, the gastric viscera, etc., and all will be to you only a confusion of symptoms, which, not being united in one point, will necessarily present only a train of incoherent phenomena. Open a few bodies and this obscurity will soon disappear, which observation alone would never have been able to have dissipated. Dissect in anatomy, experiment in physiology, follow the disease and make the autopsy in medicine. This is the threefold path without which there can be no anatomist, no physiologist, no physician."

WILLIAM BOYD

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# A Text-book of Pathology

## PART I. GENERAL PATHOLOGY

### Chapter

### 1

### THE CONTENT OF PATHOLOGY

**PATHOLOGY** is the study of the structure and function of the body in disease, just as **anatomy** is the study of normal structure and physiology the study of normal function. The changes in structure are called lesions, the changes in function may or may not appear as symptoms. Pathology is concerned with answering the questions *How* and *Why* in relation to disease. At first sight there would appear to be no difficulty in forming a concept of what we mean by disease, but the more closely the matter is considered the more difficult does it become. Health is a condition in which the organism is in complete adaptation to its surroundings. Disease is a change in that condition as a result of which the organism suffers from discomfort (*dis-ease*). As Virchow put it: "Disease is life under altered conditions." But the question of health or disease may be considered from the point of view of the physician or of the pathologist, and the result will be correspondingly different. A man may die from the terrible convulsions of strychnine poisoning, yet the pathologist will find no structural change or lesion to which he can point as the cause of death. On the other hand a person in perfect health may be found at autopsy to have a tuberculous lesion of the lung or chronic disease of the heart valves which has been compensated for by cardiac hypertrophy. Are we to consider such a person in a state of health or of disease? It has been said that "health is harmony, disease discord," and Adami remarks that the harmony may be in a minor key. So long as there is harmony, even though the price of that harmony be the structural alterations of compensation and resistance, the person is in a state of health to the clinician, but to the pathologist the lesions in the organs have to be interpreted as evidence of disease.

Clinical medicine is concerned with disturbances of function as manifested by the symptoms of the patient, while pathological anatomy is concerned with changes in structure. But it is essential that the two go hand in hand, for both present only one side of the picture. The pathologist performing an autopsy on a case of typhoid fever for the first time could no more deduce the clinical symptoms from the lesions which he finds after

death than could the clinician forecast the structural changes from a study of the living typhoid patient if he had never attended an autopsy. The pathologist who never goes on the wards is comparable to the clinician who never enters the autopsy room.

Pathology, then, in the sense of morbid anatomy and morbid histology, is the study of the tissue alterations which develop as the result of pathogenic or disease-producing agencies. It is true that in actual practice these alterations may be of so fine a character as to escape detection, but this is merely because the methods at our disposal are still comparatively crude. This is even more true of the so-called functional disorders which form so large a part of the physician's practice. In spite of these limitations it can still be said that pathology is the substructure of diagnosis, for, as Hamman points out, diagnosis is concerned more with structural change than with functional disturbance.

It is easy to make the fatal mistake of regarding pathology as being concerned merely with states, particularly the state at the moment of death. But disease is not a state; it is rather a *process* ever changing in its manifestations, a process which may end in recovery or in death, which may be acute and fulminating in its manifestations, or which may represent the slow ageing of the tissues brought about by the sharp tooth of time. To rest content with recognizing and correctly naming a mitral stenosis at autopsy is to be satisfied with playing the part of a technician. For the lesion has been present during many years of life, and its presence is not sufficient to explain the final end. Moreover the pathologist has to try to explain not only why the patient died but how he was able to live. As Boycott remarks: "I do not wonder that people die; that is easy enough. What I marvel at is that they go on living with bodies so maimed, disordered, and worn out." We must concern ourselves with processes which have got out of place, out of time, and out of tune, as well as with disorder of structure, for disease may be defined as merely a summation of chemical reactions that have gone wrong. It is the high function of the pathologist not merely to attach correct labels to the lesions when he sees them, but to reconstruct the course of events from the earliest inception of the disease to the final moment when we have to fall out of "the splendid procession of life." In speaking of the microscopic study of the kidney from a case of chronic Bright's disease, Rich paints a picture of the true pathologist: "In that minute film of tissue he plainly sees dynamic disturbances of renal function with alterations in the composition of the blood, the tissue fluids, and the urine, the elevated blood-pressure, the hypertrophied heart with its constant threat of decompensation, the anemia with its debilitating effects, the disturbances of vision, the impending symptoms of uremia. In brief, in that bit of dead tissue, altered by the effects of fixatives and stains, he sees the general outlines of a living patient progressing along the path from health to death."

But the lesions and the functional disorders to which they give rise are not everything. There are the hidden qualities of tissue and blood to be considered, those qualities which determine the result, favorable or otherwise, of the interaction between the patient and noxious influences. The more searching the inquiry, the more difficult becomes the separation of

the concepts of health and disease, till finally there is danger of arriving at the conclusion that all things medical belong to the pathologist.

The structural changes observed at autopsy are not due to death, for if death be sufficiently sudden, as from poisoning by prussic acid, no change of any kind may be detected. They are the result of the processes of degeneration, reaction, repair, and growth disturbance which have preceded death. Pathology is therefore concerned with a study of these processes and with their causes. They may be grouped under a comparatively few headings, and a study of these general processes comprises the subject of General Pathology which forms the first part of this book. After completion of this study it is possible to turn to the various organs and systems and apply the general principles to specific instances. The study of heart disease, kidney disease, nervous disease, etc., comprises the subject of Special Pathology.

Finally the student must keep in mind the fact that what is usually called morbid anatomy constitutes only one part of the general subject of pathology, although it is the part with which this book is primarily concerned. The modern term psychosomatic medicine is an indication of the tardy realization of this truth, a truth of which the greatest physicians have always been aware. For it is the whole patient who comes to the doctor's office, not just a disordered liver, a cardiac lesion, or a septic throat. As Paracelsus remarked in the sixteenth century, he who wants to know man must look upon him as a whole, not as a patched-up piece of work. Man is more than a sum of his parts. In the words of an old French proverb: "There are no diseases, but only sick people." It has been estimated that at least 50 per cent of all patients consulting a physician have no real organic trouble. The young recruit waiting to make his first parachute jump often has albumen and red blood cells in the urine and no eosinophils in the blood, but the real disturbance is in his mind rather than in his kidney or bone marrow. Plato's profound remark in the *Phaedrus* is as true today as when it was first uttered. "For this is the great error of our day in the treatment of the human body, that physicians separate the soul from the body."

#### ADDITIONAL READING

ADAMI: Principles of Pathology. Philadelphia, 1910, p. 21

BOYCOTT: *Lancet*, 1933, 2, 846.

HAMMAN AND RICH: Clinical Pathologic Conference, Internat. Clinics, 1933, 1, 198.

## Chapter

## 2

# DEGENERATIVE PROCESSES AND DISTURBANCES OF METABOLISM

THE group of processes known to pathologists as the degenerations forms rather a heterogeneous collection. They can be studied from the point of view of the abnormal materials which appear in the cells or the intercellular substance. It is better to take a wider view and regard them as indications of sickness on the part of the cells, as disorders of metabolism which suggest what Galton has called the steady and pitiless march of the hidden weaknesses in our constitution. They are the fingerprints of disease left on the tissues. Some are slight and transitory; others proceed to a fatal termination.

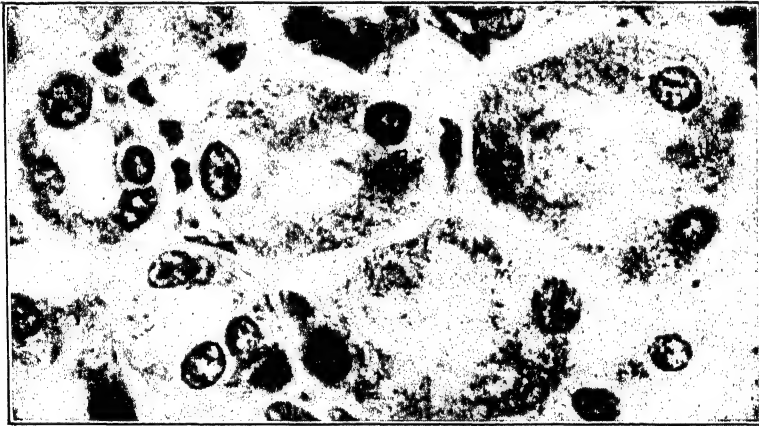


FIG. 1.—Cloudy swelling of kidney. The cells of the convoluted tubules show marked swelling and granularity, while those of the collecting tubules (at the left) are but little affected.  $\times 1000$ .

### CLOUDY SWELLING

The condition known from its gross appearance as cloudy swelling, also called *albuminous degeneration*, is much the commonest of the degenerations. It is an indication of a disturbance of cell metabolism which may occur as the result of any toxemia. The toxin may be the product of any infection or infectious fever such as pneumonia or septicemia.

The principal organs showing cloudy swelling are the kidney, the liver, and the heart muscle. The organ affected is slightly enlarged, owing to

swelling of the cells of which it is composed. It is pale, the bloodvessels being compressed by the swollen cells. The cut surface has a rather cloudy appearance, slightly opaque, as if scalded in hot water.

The *microscopic appearance* can best be studied in the highly specialized cells of the convoluted tubule of the kidney. (Fig. 1.) The cell presents two abnormal features: (1) it is unduly granular, and (2) it is swollen so that it projects unevenly into the lumen of the tubule. As the condition advances the cell may break down and the granular material is discharged into the lumen of the tubule. The granules are albuminous in character, and can be distinguished from fatty granules by the fact that they are soluble in acetic acid and insoluble in lipid solvents such as chloroform. Part at least of the granular appearance seems to be due to changes in the mitochondrial rods, which break up into granules that fuse to form larger masses. The swelling of the cell is due to edema.

**HYDROPIC DEGENERATION.**—In this condition, also called serous degeneration, epithelial cells become distended with clear fluid, sometimes to such an extent that they actually burst. The change is best seen in acute inflammation of surface epithelium, as in blisters, smallpox, and anthrax. The osmotic pressure of the cytoplasm is altered, so that the cells take up fluid from the surrounding tissue. Detached cells lying in watery fluid undergo a similar change. The cells of a carcinoma, especially carcinoma of the cervix, may show marked hydropic degeneration.

## FATTY DEGENERATION

Fatty degeneration is a condition in which degeneration of the cell is accompanied by the appearance of fat droplets in the cytoplasm. As we proceed we shall find that this definition says too much and at the same time too little. The presence of visible fat in cells where it normally cannot be seen is of twofold interest: (1) it is a sure indication that the cell is sick (except in the case of the liver), and (2) the fat itself is a substance singularly interesting to study and easy to demonstrate.

Fat is present in the body in two very different forms: (1) as depot fat, and (2) as tissue fat. The depot fat is visible fat giving the usual chemical reactions, and collected chiefly in the subcutaneous tissue and the omentum, where it is known as adipose tissue. The fat cell of adipose tissue is a connective-tissue cell distended with neutral fat which displaces the nucleus to the side of the cell. In malnutrition the fat cells are much smaller than when a person is well nourished. As the result of insulin and glucose therapy the diameter of the fat cells may be doubled; before treatment they may be small and thick-walled, while after treatment they become distended and thin-walled. In the fetus the fat cell at first has a central nucleus and granular cytoplasm. Fine globules of fat appear in the cytoplasm around the granules, enlarge, and coalesce so as to form one large globule which occupies the entire cell. In areas where adipose tissue has been destroyed the new cells are sometimes of the fetal type at first. The tissue fat exists in a combined or invisible form so united with the protoplasm of the cells that it cannot be demonstrated by histological methods unless it becomes visible as the result of pathological change. For long the question was asked: Where does this tissue fat come from? It used to be thought that the cell proteins could become changed into fat: It now appears likely that there are two great sources of fat: (1) the fat in the food and that in the fat depots, and (2) the carbohydrates.

**STAINING METHODS.**—The various methods for the demonstration of lipins (neutral fat and lipids) are of particular importance, and must be thoroughly understood by the student of fatty degeneration. In the first place it is evident that the ordinary methods of paraffin and celloidin embedding are not permissible, for they entail the use of such fat solvents as chloroform, xylol, and ether. Frozen sections are therefore used for this work. By some methods to be considered presently it is possible to convert the fat into an insoluble form, after which paraffin or celloidin embedding may be used.

The simplest staining method is the use of the azo series of *aniline dyes*, Sudan III or Scharlach R (scarlet red), on frozen sections which may be fresh or fixed in formalin. The Sudan gives an orange color, the scarlet red a brilliant red. There is no chemical union between the fat and the dye; the latter is more soluble in fat than in alcohol, so that it leaves the alcoholic solution and becomes dissolved in the fat. Cholesterol and its ester stain less brilliantly than neutral fats with scarlet red. These dyes do not stain normal myelin nor the fatty acids, but when the myelin is broken down it is readily stained. A fatty acid can be stained by any *basic aniline dye* such as methylene blue or methyl violet. The fat is first hydrolyzed into a fatty acid and glycerin by the action of dilute acid or even by exposing the section to the CO<sub>2</sub> of the air. The *oxazine dyes*, of which Nile blue sulphate is the chief one used, act as double stains. One stain is an oxazine base and stains fatty acids blue in the usual way. The other stain is formed by decomposition of the oxazine base in watery solution with the formation of a bright red dye which is soluble in neutral fat though chemically indifferent to fatty acids. By this method of Lorrain Smith the constituents in a mixture of neutral fat and fatty acids can be stained separately.

The use of *osmic acid* is the oldest method of staining fat and it is still one of the most useful, particularly for recent degenerations of the nervous system. The substance is really a peroxide of osmium which is reduced by the fat, and forms a black compound with it, which is insoluble in xylol. Thus osmic acid is a fixative as well as a stain, and tissue thus fixed can be embedded in paraffin and cut without losing its fat. Osmic acid stains neutral fat and lipids such as cholesterol ester and myelin, but the tissues must not be kept too long in formalin, else they will become oxidized.

The *Marchi* and the *Weigert* methods of staining are of great value for the study of the lipids in disease of the central nervous system. These methods are described in Chapter 31.

Another method of great value in differentiating lipids from neutral fats is *examination by polarized light*. When Nicol's prisms are placed on the microscope and a frozen section is then examined, cholesterol and cholesterol ester which are anisotropic, *i. e.*, doubly refractile, appear as brilliant bodies against a black background, the ester often taking the form of a Maltese cross of light. Neutral fats are not anisotropic, and therefore remain invisible. This method is sometimes very useful in pathological conditions.

**The Nature of Fatty Metamorphosis.**—From the days of Virchow a distinction has been drawn between two forms of fatty change: (1) fatty degeneration, and (2) fatty infiltration. These may both be included under the term fatty metamorphosis. In fatty degeneration according to Virchow, owing to disease of the cell the proteins of the cytoplasm were converted into fat, whereas in fatty infiltration too much fat was carried to an otherwise healthy cell and appeared there in visible form. Dible, who has studied the matter very thoroughly, believes that fatty change in the liver is entirely due to transfer of fat from fat depots, and is therefore in the nature of an infiltration. In experimental starvation the liver quickly becomes

fatty, the degree of the change depending on the amount of available fat in the body. When an animal is starved until the fat in the depots is exhausted, poisoning with phosphorus fails to produce fatty degeneration of the liver. It seems probable that the factor of starvation plays a part in the genesis of many cases of fatty liver owing to interference with metabolism there. In other organs, *e. g.*, heart muscle and kidneys, a similar mechanism seems to be responsible for the fatty change. The old idea of *fat phanerosis* (*phaneros*, visible), an unmasking of the invisible fat already present in the cytoplasm of these organs, must now be replaced by the concept of fatty infiltration (Popjak). The experimental work of Dible and Govan shows that "fatty degeneration" of the heart and kidney may be produced by the intensive administration of fat in the diet. In such cases the fatty metamorphosis appears to be an infiltration rather than a degeneration.

**Causes.**—There are two great *causes of fatty metamorphosis*: (1) the action of toxins, and (2) lack of oxygen. It is possible that the first factor acts by virtue of interfering with the proper oxygenation of the cell, which would make this the basis of all fatty degeneration. The poisons may be divided into organic and inorganic. The organic poisons are bacterial toxins, by far the most important etiological factor. Any of the acute infections or such a chronic infection as tuberculosis may act in this way. Of the inorganic poisons phosphorus, chloroform, and alcohol are the most important. Phosphorus poisoning is seldom seen nowadays. If a person dies some days after prolonged chloroform anesthesia, marked fatty degeneration particularly of the liver will be found. These metabolic disturbances are the basis of the so-called delayed chloroform poisoning. Chronic alcoholics, especially heavy beer-drinkers, may show marked fatty degeneration of the liver. Insufficient oxygenation as a cause is seen in severe anemias both primary (pernicious) and secondary. The degeneration which is well seen in the heart and kidney as well as the liver is most marked in pernicious anemia.

The *causes of lipomatosis* or adiposity are: (1) excessive ingestion of fats and to a lesser degree of carbohydrates, and (2) factors which interfere with the proper utilization of fat. Among the latter are lack of exercise, advancing years, sex (female), race (Hebrew), and sometimes dysfunction of one of the ductless glands, particularly the pituitary as in the disease known as *dystrophia adiposo-genitalis*.

**Fatty Degeneration in Special Organs.**—Although fatty degeneration may affect the cells of any organ, it is most readily observed in the liver, the kidney, and the heart.

The *liver* is paler and yellower than normal, soft in consistence, the edges are swollen and rounded, and the cut surface may be slightly greasy. The organ may be considerably enlarged, as in the beer-drinker's liver. Microscopically the liver cells are filled with fat droplets which can be readily stained with Sudan, osmic acid, and the other methods already described. (Figs. 2 and 3.) All of the fat is neutral fat. As Hartroft points out, many of the fat vacuoles are so huge that they could not represent single distended liver cells; they are fat cysts formed by the fusion of many distended cells. Marked fatty changes in the liver are seen in severe anemia, pulmonary



tuberculosis, diabetes, and chronic venous congestion of the liver, conditions in which oxidation of the fats is interfered with. The liver plays an important part in the oxidation of fats and the formation of ketone bodies. The multiplicity of conditions which will cause fatty metamorphosis in the liver suggests that one of the most easily disturbed properties of the liver cell is its ability to deal with fat. The less the oxidation, the greater is the accumulation of fat. If an animal is first starved it is impossible to produce fatty changes in the liver by the ordinary experimental methods, as no fat is transported from the depleted depots.

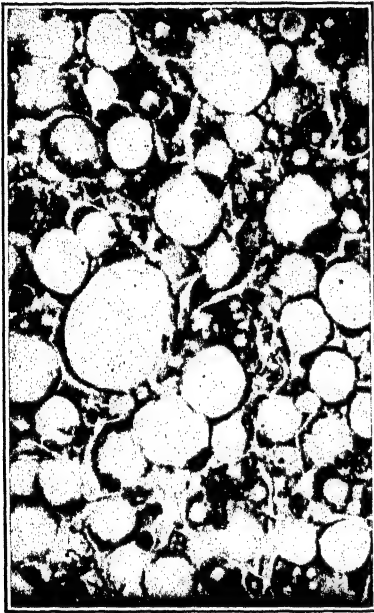


FIG. 2.—Fatty liver. Great numbers of fat-filled cells and some larger fat cysts.  $\times 375$

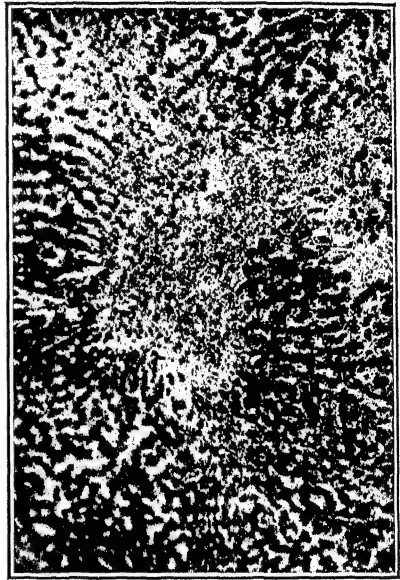


FIG. 3.—Fatty liver stained with osmic acid. The fat is at the periphery of the lobules.  $\times 75$ .

In recent years much interest has been aroused by the so-called *lipotropic factors*, a term suggested by Best to indicate substances which prevent or remove the accumulation of excess fat in the liver. Under normal conditions the amount of fat in the liver is fairly constant. An accumulation of fat indicates a change in metabolism. This may be due to failure in the transport of fat from the liver or to too rapid withdrawal from the fat depots for the liver to deal with. Phospholipids are essential for the transport of fat, and as choline promotes the formation of phospholipids absence of this food factor from the diet leads to the rapid accumulation of enormous amounts of fat in the liver. This is true also of choline precursors such as methionine. The effect of protein on fat transport seems to be due to the transfer of methyl groups from methionine for the synthesis of choline. Pregnancy damages the liver because the lipotropic factors are sidetracked

# PLATE I



Fatty Degeneration of Heart

The majority of the muscle cells are loaded with fat stained red with Scharlach R.

to the fetus. Dietary casein has a lipotropic effect; it is possible that this may be due to its methionine content. Another lipotropic factor named lipocaic has been extracted from the pancreas.

Accumulation of fat in the liver can be produced experimentally in a variety of ways: (1) by the absence of such lipotropic factors as choline, methionine, betaine, and inositol; (2) by pancreatectomy; (3) by the administration of toxic substances such as chloroform; (4) by a high fat-low protein (casein) diet; (5) by anterior pituitary extract (ketogenic fraction). All fatty livers are not alike, and the effect of lipotropic factors depends on the character of the lipids. Thus choline does not prevent fat accumulation due to anterior pituitary extract but lipocaic does, nor does choline have much effect on the fatty livers due to toxins and starvation. For further information on these matters the reader is referred to the reviews by Best and by McHenry and Patterson.

Fatty infiltration of the liver caused by a high fat-low protein (casein) diet tends to lead to cirrhosis (fibrosis). This may be associated with necrosis of the liver cells or may be independent of it. There is apparently direct stimulation of the fibroblasts with resulting cirrhosis.

The *kidney* is pale, but is not necessarily enlarged. The cells lining the convoluted tubules contain large numbers of small fat droplets. This fat is chiefly lipid in the moderate grades of degeneration, although neutral fats appear in the more severe forms. The droplets first appear between the nucleus and the base of the cell, but presently they may fill the entire cell. As the condition is a true degeneration the nucleus and cell structure may show degenerative changes in the advanced stages.

In the *heart* fatty degeneration is especially marked in pernicious anemia and other severe forms of anemia. The heart is soft and flabby so that in extreme cases it may collapse in mushroom fashion when held up by the apex. The change is best seen in the papillary muscles of the left ventricle, where it produces a speckled appearance of the muscle under the endocardium, to which the names of "thrush breast" and "tabby cat" have been applied. Other parts of the wall of the ventricles may also show marked mottling. Under the microscope the change is seen to be due to a replacement of the muscle fibers (which are really cells) by numerous droplets of fat often arranged in longitudinal rows. (Plate I) Normal heart muscle contains no visible fat, and yet it yields 15 per cent of fat when extracted with ether. A heart the seat of marked fatty degeneration is full of visible fat, yet extraction with ether may show only a very slight increase.

In a *medullated nerve* the fatty metamorphosis known as *Wallerian degeneration* may occur as the result of injury to the nerve fiber either in a peripheral nerve or in the central nervous system. The myelin becomes broken up into droplets which can be beautifully demonstrated by means of Marchi's method. This change will be described in detail in the section on the Nervous System.

*Lipomatosis* is a local adiposity of the connective tissue due to fatty infiltration. It is best seen in the heart, where large droplets of fat lie in the connective tissue between the muscle bundles, and may interfere considerably with the action of the organ. If the extra supply of fat is cut off the lipomatosis will disappear.

**Lipoidal Degeneration.**—In ordinary fatty degeneration and infiltration the fats concerned are neutral fats. There is in addition an important group of pathological changes involving the lipids, mainly cholesterol and cholesterol ester. These lipoidal changes may be both in the nature of degeneration and infiltration. Cholesterol, which is not a true fat but an alcohol, is a constituent of all the cells of the body, but in an invisible form. When the cell undergoes autolysis the cholesterol is not destroyed, so that it may become visible either as a needle-shaped crystal or as a flat plate with one corner bitten out. The nature of these crystals as well as that of the ester can be beautifully demonstrated by examining frozen sections under crossed Nicol's prisms; the brilliantly white anisotropic material stands out against the black background. Cholesterol crystals may be found in caseous tissue, infarcts, old hemorrhages, atheroma, degenerating goiters, dermoid cysts, hydrocele fluid, etc. The yellow patches on the inner surface of the aorta in atheroma consist mainly of lipids, but neutral fats are also present. The characteristic spindle-shaped clefts in the tissue are often associated with giant cells, indicating a foreign body giant cell reaction. This reaction is best seen in the tumor-like masses called xanthomas. The cholesteatomatous masses which occasionally occur in the ear and the cranial cavity consist largely of cholesterol. Two conditions which more closely resemble true fatty degeneration than those already mentioned are cholesterolosis of the gall-bladder (strawberry gall-bladder) and those forms of Bright's disease which are associated with marked albuminuria and edema, *i. e.*, nephrosis and wet nephritis. In these conditions there is a remarkable collection of cholesterol in the epithelial cells of the gall-bladder and kidney respectively, which will be considered in detail when these diseases are described. When cholesterol ester is set free as the result of lipoidal degeneration it is often taken up by phagocytic cells, giving the cytoplasm of these cells a vacuolated appearance. These *foam cells* are seen to best advantage around an area of brain softening, but they are found in degenerating goiter and many other situations.

Tissue reactions to lipids, a term which signifies a heterogeneous group that includes fats, oils, waxes, phospholipids and sterols, are varied. These reactions occur when the fats are not completely metabolized. The reaction about unhydrolyzed fat is similar to that against an inert oil-like petrolatum. With hydrolysis of the fat and liberation of fatty acids there may be acute necrosis or a non-specific reaction on the part of fibroblasts and macrophages. Insoluble soaps excite a foreign body giant-cell reaction. The various reactions have been fully discussed by Hirsch.

**PROGRESSIVE LIPODYSTROPHY.**—This strange disturbance of fat metabolism is characterized by a symmetrical and progressive loss of subcutaneous fat in the face, arms and upper part of the body, associated with undue deposition of fat in the buttocks and lower limbs, occurring in children, usually girls. In extreme cases the skin rides loosely over the muscles, giving the patient a cadaver-like expression. To the eyes of one observer the lower half of the body looked like a model of one of Rubens' paintings, while the upper half resembled one of the witches in Macbeth. The adipose tissue of the affected parts is unable to store fat, no matter how much the patient may eat. The cause is unknown.

**INSULIN LIPODYSTROPHY.**—A local atrophy of subcutaneous fat may follow the prolonged use of insulin if it is injected continually in the same area. This may be due to a lipase in the insulin or to damage to the fat envelopes. There may be a local infiltration of lymphocytes and plasma cells.

### GLYCOGEN INFILTRATION

Glycogen is the storage form of carbohydrates, and corresponds to the starch of plants. It occurs in the body in a labile and a stable form. The labile form, which represents by far the greatest amount, is present in abundance in the liver (38 per cent of the total amount in the body) and in the muscles (44 per cent). It is converted into glucose with great ease, and rapidly disappears from the tissues after death. As it is soluble in water, the tissue should be fixed in alcohol. The stable form occurs in minute quantity in many tissues, and under pathological conditions it may be greatly increased in amount. Glycogen is the only carbohydrate which can be demonstrated under the microscope, and is of particular interest on that account. It is colored reddish-brown with iodine, and is beautifully shown by Best's carmine stain which colors it crimson. Even better is the McManus PAS stain (periodic acid-leukofuchsin reaction of Schiff) with diastase digestion of duplicate slides as a control.

Under pathological conditions there may be an increase (infiltration) or diminution in the amount of glycogen in the tissues. In *diabetes* the depot glycogen is rapidly converted into glucose, so that there is a marked diminution in the amount in the liver and muscles. Large amounts of glycogen occur in the heart in diabetes, and also frequently in normal infants. Large deposits appear in the epithelium of the renal tubules, especially the loop of Henle (Fig. 4), probably owing to absorption of glucose from the sugar-loaded urine. In *suppurations* the polymorphonuclear leukocytes both in the blood and the pus contain an excess of glycogen (iodophilic granules). Glycogen is likely to appear in places which show a pathological increase of fat, and probably from similar causes. It is abundant in some *tumors*, especially in hypernephroma (a malignant tumor of the kidney), where the cells have a highly vacuolated or characteristically clear appearance, due to the presence of fat and glycogen, which are present in varying proportions.

**GLYCOGEN ACCUMULATION DISEASE OR VON GIERKE'S DISEASE.**—This is a strange condition in children, characterized by an excessive storage of glycogen, especially in the liver and to a lesser degree in the kidney. The liver becomes enormous, and this great hepatomegaly in a child unaccompanied by splenomegaly, jaundice, or any marked constitutional disturbance is highly characteristic. There is hypoglycemia, but without the usual clinical symptoms. The injection of adrenalin fails to mobilize the glycogen in the liver as it should do in a normal person. Acetone and diacetic acid may be present in the urine but without glycosuria. The cause of this ketosis is fundamentally the same as that of diabetes, although brought about in a different way. In diabetes the sugar, although present in abundance in the blood, is unable to play its proper part in the combustion of fats. In this disease the fats are not properly burnt because the sugar is held in the liver in the form of glycogen. The liver cells are greatly distended, the cytoplasm clear or vacuolated and, in one case which I studied, the cell boundaries in many places appeared to be broken down (Fig. 5). In von Gierke's original case the kidneys were markedly enlarged owing to accumulation of glycogen in the epithelium of the convoluted

tubules. Pompe has described under the title of idiopathic hypertrophy of the heart a case of enormous enlargement of the heart in a young boy in whom the heart muscle fibers were hugely distended with glycogen. The disease appears to depend on a defective transformation of glycogen into glucose owing to absence of the normal glycogenolytic enzyme, so that it accumulates in the glycogen depots. The condition is, therefore, analogous to the lipid storage disease (Gaucher's disease, Niemann-Pick's disease, Christian's syndrome) in which the cells of the reticulo-endothelial system become loaded with lipid. Glycogen storage, like lipid storage, may show a familial tendency and may be regarded as a congenital anomaly of metabolism.



FIG. 4.—Glycogen represented by clear spaces in renal tubules in diabetes.  $\times 225$ .



FIG. 5.—Von Gierke's disease. Liver cells distended with glycogen, which has been dissolved out.  $\times 400$ .

An analysis of the whole subject of glycogen storage disease will be found in the papers of van Creveld, who, it may be noted, reported two clinical cases one year before the publication of von Gierke's autopsy report.

### AMYLOID DEGENERATION

A remarkably interesting though nowadays rather uncommon degenerative process is that known as amyloid degeneration. It differs fundamentally from fatty degeneration in that it affects the ground substance of connective tissue and not the parenchymatous cells of an organ, although the latter may undergo secondary changes.

**NATURE OF AMYLOID.**—Amyloid is a mucopolysaccharide-protein complex. Alterations in either constituent of the complex may lead to deposition of amyloid in the ground substance. The mucopolysaccharide is chondroitin sulphuric acid, the sulphated form of the hyaluronic acid which forms normal ground substance. The most characteristic of all the staining reactions, that with methyl violet, is dependent on the presence of this acid. The acid occurs principally in cartilage and in organs rich in elastic tissue such as the lung and aorta. Amyloid disease is commonly associated with long-continued destruction of such tissues, *e. g.*, chronic osteomyelitis, suppurative arthritis and pulmonary tuberculosis. Rare amyloid "tumors" are found in relation to the nasal septum, larynx and bronchi, all of which are rich in cartilage. Some of the earliest lesions appear in the arteries, with their abundant elastic tissue. Sometimes disturbance in the protein fraction, possibly globulin, may be of importance, as amyloid may develop in allergic states (antigen-antibody reactions involving the globulins), and in multiple myeloma, a condition in which hyperglobulinemia is an important feature. As the so-called "collagen diseases" consist essentially in an alteration of the acid mucopolysaccharides of the ground substance, it seems reasonable to link them with amyloid disease.

The views of Teilum on the nature and production of amyloid are worthy of consideration. According to Teilum the protein constituent (globulin) is dependent on disturbance of mesenchymal cells, particularly reticulo-endothelial cells and plasma cells, the health of which is maintained by the interaction of cortisone or some related adrenal cortical hormone and ascorbic acid. These cells are believed to be connected with the production of gamma globulin, and hyperglobulinemia is often associated with amyloidosis. Diseases of the mesenchyme in which there is disturbance of enzyme systems such as hyaluronidase and ribonuclease seem to be influenced by the interaction of cortisone and ascorbic acid. It is therefore of interest that in 20 out of 32 cases of rheumatoid arthritis Teilum found amyloid deposits either mild in degree or marked.

The cytoplasm of plasma cells is colored red with pyronin with the pyronin-methyl green stain, and in the early stage of amyloid disease other mesenchymal cells, such as those of the reticulo-endothelial system, also show pyroninophilia. It is significant that pyroninophilia is an indication of the synthesis of ribonucleic acid in cytoplasm. Teilum believes that pronounced pyroninophilia is fundamental in the pathogenesis of amyloid. It occurs in the same sites as amyloid deposits.

The continued administration of casein to mice is followed by amyloidosis (see below). If before the appearance of amyloid cortisone is injected for a few days there is an immediate deposition of amyloid in the spleen and the other usual sites of the disease. Cortisone and ascorbic acid appear to have contrasting effects, ascorbic acid leading to the production of pyroninophilia, the synthesis of ribonucleic acid, and an elevated gamma globulin, whilst cortisone results in the deposition of amyloid. Amyloidosis occurs in guinea pigs on a diet deficient in ascorbic acid.

The interest of these experimental observations is that they link amyloidosis with protein synthesis by mesenchymal cells, the process being apparently controlled by the interaction of ascorbic acid and an adrenal cortical hormone resembling cortisone.

**Causes of Amyloid Disease.**—In the great majority of cases amyloid degeneration occurs in chronic cachectic conditions associated with marked loss of albumen from the body. Examples of such conditions are chronic tuberculosis (lungs, bones), long-continued suppuration, and breaking down syphilitic gummata. In multiple myeloma of bone, masses of amyloid may occur in the muscles and elsewhere. This observation is of interest because the cells of multiple myeloma are plasma cells, and hyperglobuline-

mia is a feature of the disease. Sometimes no adequate cause can be found even at autopsy.

The experimental production of amyloidosis is interesting, though it cannot be said to have thrown much light on this dark subject. The condition can be produced in many different animals and in a variety of ways. The injection of bacterial toxins over a period of months may lead to amyloid degeneration, although by no means invariably. A broth culture of *Staphylococcus aureus* has been much used. Horses injected with diphtheria toxin for the production of antitoxin may develop amyloid. Mice with transplanted malignant tumors may show amyloidosis. The subcutaneous injection of nutrose (sodium caseinate) into mice is the most effective and rapid way of producing amyloidosis.

**STAINING REACTIONS.**—There are two special methods by which amyloid can be stained: (1) iodine, (2) methyl violet.

*Iodine* in watery solution, conveniently used in the form of Lugol's solution, stains amyloid a mahogany brown when viewed by reflected light, the surrounding tissue taking on a yellow color. The method is very useful in the autopsy room for determining if an organ contains amyloid; the solution of iodine is poured over the cut surface, and in a few minutes the dark brown patches of amyloid will appear. The renal glomeruli form a striking picture when the kidney is treated in this way. The method can be used for microscopic sections, the amyloid again appearing dark brown by reflected light, *i. e.*, when the mirror is not used. When viewed by ordinary transmitted light it is a pale orange. If the iodine is followed by 1 per cent sulphuric acid, the brown may turn a light blue. This reaction which is responsible for the name amyloid is quite variable. Moreover the reaction with iodine itself is often not given in the early stages of the disease, suggesting that the amyloid may undergo some chemical change as it matures. The iodine reaction is apt to fail in tissue which has been kept for a long time in formalin.

*Methyl violet* and gentian violet give a metachromatic reaction which is the best and most constant method of demonstrating amyloid. It acts well on tissue which has been kept long in formalin. With this method the amyloid stains a rose red due to the chondroitin-sulphuric acid, while the surrounding tissue is colored bluish violet. This metachromatic reaction is best obtained with frozen sections and is most clearly seen with artificial light.

*Congo red* stains amyloid in the living body. When this dye is injected into the blood stream of an animal with amyloid disease, all the amyloid is found to be stained bright red at autopsy. This method can be applied to the *clinical diagnosis* of doubtful cases, the amount of dye removed from the blood by the amyloid being measured at the end of an hour. By means of the Congo red test it has been shown that amyloid may be removed from an organ if the cause responsible for it can be removed. The dye can be used as a microscopic stain if the tissue is fixed in corrosive sublimate before staining.

**Changes in the Organs.**—Amyloid degeneration is a widespread condition very rarely confined to a single organ, and may well be called general amyloidosis. The organs chiefly affected are the liver, spleen, and kidney, the change usually beginning in the spleen. An additional group of three comprises the adrenals, the pancreas, and the intestinal mucous membrane. In addition to these almost every organ in the body may show some degree of change. It is the ground substance of the organs, particularly in the media of the arterioles, which is attacked. The affected tissues undergo



a hyaline homogeneous swelling, so that the organ looks as if molten wax had been poured into the interstices and had hardened there. As a result of this swelling the parenchymatous cells become compressed and atrophic. The walls of the small vessels are thickened and their lumen may be greatly narrowed. The liver and spleen are enlarged, dense and elastic, resembling hard India rubber, the edges remaining hard and sharp in contrast to the rounded contours of the fatty liver. The cut surface is smooth, and has a translucent waxy appearance, so that the condition is sometimes known as waxy degeneration. In the kidney other degenerative changes complicate the picture, so that its gross appearance will be described separately.

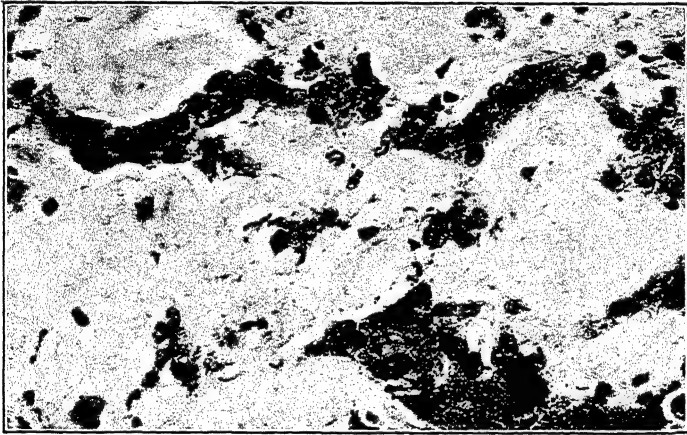


Fig. 6.—Amyloid degeneration of liver. The liver cells are greatly compressed by the abundant amyloid material.  $\times 350$ .

The *liver* is enlarged, sometimes to a great degree. It seems to have been fixed in formalin, so firm is its consistence and so sharply marked its borders, but it is elastic rather than hard. The cut surface presents the usual translucent appearance. Microscopically, the change commences in the intermediate zone of the lobule. The amyloid appears between the sinus endothelium and the liver cells. This tissue becomes enormously swollen, so that on the one hand the liver cells are so compressed that they atrophy and may finally disappear, while on the other hand the sinusoids become narrowed. (Fig. 6.)

The *spleen* is also enlarged, firm, elastic, and translucent. The amyloid may be distributed in two ways. In the common form it appears in the walls of the arteries in the Malpighian bodies (Fig. 7) and these lymphoid masses are gradually replaced by translucent masses of amyloid which are scattered over the surface like grains of boiled sago, so that this form is known as the *sago spleen*. (Fig. 8.) In the rarer form, the *diffuse amyloid spleen*, the change affects the connective tissue of the venous sinuses and the reticulum of the pulp, so that the enlargement of the organ is much greater.

The *kidney* presents a special problem because of secondary changes. It may be enlarged like the liver and spleen, or normal in size, or even contracted. Fatty degenerative changes in the tubules are common, and these interfere with the waxy look of the cortex, giving it a streaked or spotty appearance. Microscopically the change begins in the connective tissue of the vessels in the glomerular tufts, and also involves the walls of the arterioles and the connective tissue under the basement membrane of the collecting tubules. When a solution of iodine is poured over the cut surface the affected glomeruli stand out as little brown dots. The glomeruli become converted into masses of amyloid, as a result of which all circulation

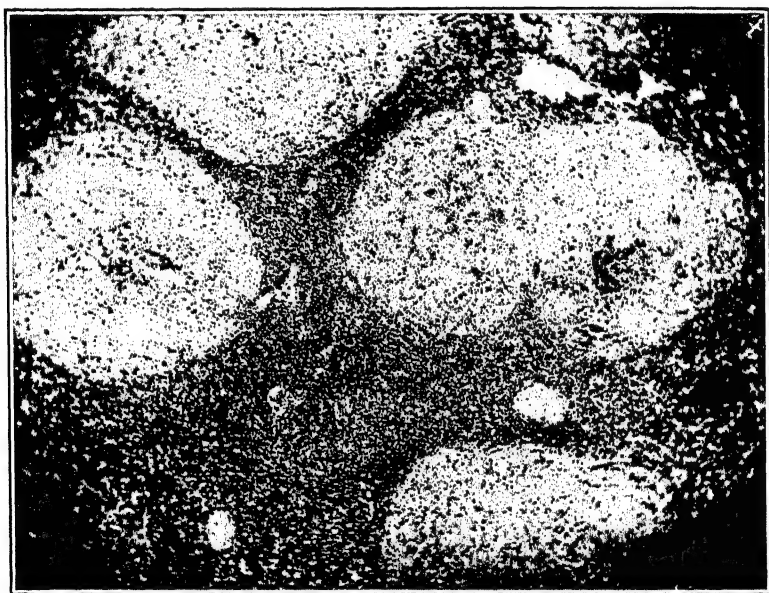


FIG. 7.—Sago spleen, showing large masses of amyloid.  $\times 45$ .

through the glomerulus may be stopped, but usually some patent vessels still remain. Owing to obstruction to the glomerular circulation the convoluted tubules are deprived of their blood supply and may undergo degenerative changes with great accumulation of lipid, so that the condition has been called amyloid nephrosis. It is these tubular changes which are responsible for the gross appearance already described. The tubules may gradually atrophy and be replaced by fibrous tissues, which by shrinking produce a picture of a contracted kidney like that of chronic Bright's disease.

Many *other organs* may show the amyloid change. The adrenals may be converted into solid masses of amyloid so that they become considerably enlarged. In the intestine the change affects the connective tissue in the villi (Fig. 9), so that when treated with iodine the mucosa may have an appearance of brown velvet. The thyroid may be converted into an almost

solid mass of amyloid. The heart may be the seat of extensive amyloid deposits between the muscle fibers.

**PRIMARY OR ATYPICAL AMYLOID.**—The amyloid disease described above is referred to as secondary, because there is usually an obvious primary cause. There is another and more indefinite group of cases which, being without obvious cause, are termed primary. As the reactions with amyloid stains are variable and capricious and as the distribution is not in the usual sites the term atypical is also used. Local deposits without general amyloidosis may occur in the heart and the tongue. Peculiar amyloid masses known as amyloid "tumors" are rare occurrences in relation to the nasal septum, larynx and bronchi. It would appear that in all these cases the deposits of amyloid depend on local rather than on general disturbances.

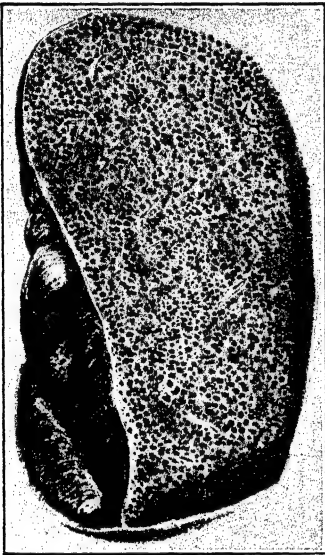


FIG. 8.—Amyloid spleen of the sago type. The numerous small areas of amyloid are stained darkly with iodine.



FIG. 9.—Amyloid degeneration of intestine. The villi are much enlarged by amyloid deposits.  $\times 60$ .

**Clinical Effects.**—General amyloidosis may or may not produce clinical effects. The organs of importance in this respect are the kidney and liver. The kidney may be large or small, depending on how far the tubular change has gone before the patient died. The clinical picture may simulate or be identical with that of glomerulonephritis. Renal edema may be associated with albuminuria and casts, or there may be signs of renal insufficiency and nitrogenous retention, with polyuria and a urine of low specific gravity and little or no albumin.

In the amyloid liver there is great narrowing or even obliteration of the sinusoids, so that ascites might be confidently expected. As a matter of fact this is so rare that one recent text-book of medicine denies its existence, but I have seen an extreme degree of ascites which rapidly reaccumulated

after tapping in an advanced case of amyloid disease of the liver, in which that organ weighed over 2500 grams.

The watery diarrhea which sometimes accompanies amyloidosis may be due to increased transudation through the diseased intestinal mucous membrane.

The *Congo red test* is of great value in clinical diagnosis. Disappearance of over 60 per cent of the dye from the blood in one hour is found only in amyloid disease. This only applies to considerable deposits of amyloid particularly in the liver. Deposits in the kidneys alone are not sufficient to give the typical reaction.

### HYALINE DEGENERATION

The changes grouped together as hyaline degeneration are in a very different category from fatty and amyloid degeneration. In the latter we are dealing with substances of a definite chemical composition, whereas in the former the composition varies widely in different cases. The term denotes a physical state rather than a chemical constitution, and includes many substances which are translucent or hyaline and stain brightly with acid dyes such as fuchsin. Hyaline degeneration affects chiefly collagenous connective tissue and the fibrous tissue in the walls of bloodvessels. This may be called connective-tissue hyaline. Other forms can be grouped together as cellular hyaline. The tissue dies before becoming changed into hyaline. *Connective-tissue hyaline* appears as a homogeneous swelling of collagen and in the walls of vessels in arteriosclerosis. It is seen in chronic malnutrition and in old age, but the exact factors responsible are not certain. The change is well seen in arteriosclerosis. In the intima the newly-formed tissue undergoes a hyaline change, and a similar change may occur in the media. The subendothelial layer of the arterioles shows marked hyaline thickening in vascular hypertension. In chronic nephritis the renal glomeruli become converted into hyaline masses. Scar tissue undergoes a similar change. The stroma of tumors may show hyaline degeneration, and the same may be seen in the reticulum of lymph nodes draining a focus of chronic inflammation. (Fig. 10.) In all of these instances the fibrous tissue loses its structure, the fibers are swollen and homogeneous, and stain red with acid stains. The appearance may resemble that of amyloid, but the material does not give the amyloid staining reactions.

*Cellular hyaline* is a heterogeneous group with no special meaning. Small hyaline masses are often seen in the cells of the renal tubules, especially in amyloid disease. The cells of the islets of Langerhans in the pancreas may become converted into a hyaline mass in diabetes. Hyaline thrombi in vessels are formed largely by fusion together of blood platelets which then undergo hyaline degeneration. *Corpora amylacea*, so-called because like starch they stain deeply with iodine (*amylon*, starch), are hyaline spherical masses made up of concentric laminae. They are seen in the normal prostate, in old infarcts of the lung, in the brain and spinal cord in old age and in degenerative conditions, and occasionally in other situa-

tions. They represent masses of degenerative cells and sometimes merely the secretion of cells. They stain deeply with hematoxylin, and have nothing to do with amyloid. In necrosis of voluntary muscle and sometimes of cardiac muscle the protoplasm may become coagulated, the striations are lost, and the fiber is converted into a swollen homogeneous hyaline mass. (Fig. 11.) This condition, known as *Zenker's degeneration*, is best seen in the rectus abdominis muscle in typhoid fever, but it is also seen in other muscles and other infections.

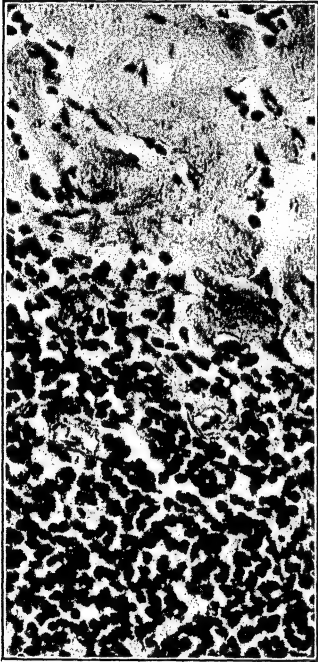


FIG. 10.—Hyaline degeneration of a lymph node.  $\times 350$ .



FIG. 11.—Zenker's degeneration of muscle in typhoid fever. The affected parts of the fibers have lost their transverse striations and are dark and swollen.  $\times 400$ .

## MUCOID DEGENERATION

Mucin is produced normally both by epithelial cells of mucous membranes and mucous glands and by certain connective-tissue cells, especially in the fetus. When the secretion of mucin is excessive and is associated with degeneration of the cells, the condition is called mucoid degeneration.

**EPITHELIAL MUCIN.**—In catarrhal inflammation of the mucous membrane of the respiratory tract, the gastro-intestinal canal, and the uterus, there is an excessive secretion of mucin, the cells are distended with this substance, and their outlines may disappear. The cells of a cystadenoma of the ovary produce pseudomucin in enormous amount so that a huge cyst may be formed; many of these cells degenerate and are cast off into the cyst. Cancer of the stomach, the large bowel, and more rarely the breast may produce mucin to such an extent that the tumor is converted into a mass of mucoid material. Mucin is a slimy substance which is precipitated

by acetic acid; it is basophilic, *i. e.*, stains with basic dyes, and gives a metachromatic reaction with toluidin blue, staining reddish-purple. Pseudomucin is not precipitated by acetic acid, and is stained by acid stains.

CONNECTIVE-TISSUE MUCIN.—The only place where intercellular connective-tissue mucin normally occurs is in the umbilical cord. The cells are stellate with branching processes and are separated by an abundance of clear mucin. This mucinoid or myxomatous degeneration may occur in the stroma of various tumors, most notably in the myxoma. In conditions of malnutrition a similar change may affect the bone-marrow, adipose tissue, and cartilage. In myxedema, a disease due to deficiency of thyroid secretion, the connective tissue of the skin and elsewhere becomes swollen and gelatinous, and in the early stages contains mucin. Mucin may be formed in the intercellular substance of synovial membranes and tendon sheaths; the development of this process is beautifully illustrated in the early stages of a ganglion of the wrist.

## GOUT

Gout is an ancient and famous disease. Its cause, however, is still a complete mystery. There is often a strong hereditary tendency. It is supposed to be a disturbance of purine metabolism. In support of this are the following facts: (1) The uric acid of the blood is above normal, and for a few days before an acute attack there is marked uric acid retention. (2) Deposits of sodium urate are a principal feature of the lesions. (3) Over-indulgence in purine-rich foods often precipitates the attacks. Beer and such red wines as port are much more dangerous than whisky; perhaps for this reason gout is a rare disease in Scotland. These facts do not constitute proof, for the blood uric acid may be equally high in leukemia and chronic nephritis, the deposits of urates are present in the joints when the patient is free from symptoms, and the acute attack may come on without obvious cause. The deposits of urates and the high blood uric acid may be merely concomitants of the disease, perhaps a result rather than a cause.

Gout may occur in chronic form, or as a series of acute attacks, each of which begins as agonizing pain in a joint, usually at night, followed by fever and chills; the joint is swollen, tender, and evidently acutely inflamed, and the blood may show a leukocytosis of 20,000 or more. It must be admitted that to be unable to offer a reasonable explanation for so dramatic a picture is unsatisfactory if not humiliating.

The joints chiefly affected are those of the big toe (metatarsophalangeal joint) and fingers and the knee-joint. In the superficial layers of the articular cartilage there are white chalky deposits of biurate of sodium rather like drops of paint, an appearance from which the name gout is derived (*gutta*, a drop). The sheaves of needle-shaped crystals are usually surrounded by an area of necrosis. It is not certain whether the necrosis precedes or follows the deposition of the crystals.

Accumulations of crystals may also occur in the periarticular tissue where they form masses known as tophi. Around these may often be seen foreign body giant cells. Similar deposits occur in the cartilage of the ear and in the eyelid. The overlying skin may become ulcerated and chalky material is discharged containing the characteristic crystals. A useful diagnostic procedure is to prick a suspected tophus with a needle, and look

for the crystals under the microscope. Deposits of crystals may occur in the pyramids of the kidney, for the most part within the collecting tubules but also between them, giving the pyramids a streaked appearance.

The use of radioactive isotopes has shown the existence of a miscible or metabolic pool of uric acid, which may vary widely with little or no change in the blood uric acid level. This pool is the amount of uric acid in the tissues which can mix promptly with uric acid injected intravenously. The course of the latter can be followed by labelling it isotopically with  $N^{15}$  and measuring the amount excreted in the urine. From this the amount in the miscible pool can be calculated. The normal average content of the pool is around 1,000 or 1,100 mg. of uric acid, of which one-sixth is in plasma water and five-sixth in extravascular water.

The pool is greatly increased in gout, often to four times the normal, even though the serum uric acid is only slightly raised. Stetten records one very severe case of 25 years' duration in which the pool on one occasion was 18,450 mg. and on another 31,000 mg. After several months of treatment with acetylsalicylic acid causing uricosuria the pool had dropped to 2,084 mg. with no change in the blood uric acid. Cinchophen, an ancient remedy for gout, the salicylates, and to an even greater degree Benemid (a caronamide) increase the excretion of uric acid in the urine, presumably by decreasing the amount absorbed by the renal tubules. Unfortunately after one or two decades of the disease the gouty patient is apt to develop renal impairment.

In the normal person all the uric acid in the miscible pool appears to be in solution, but in the gouty patient most of it is in the solid phase in the form of tophi. There seems to be a continuous process of solution and precipitation taking place between the tophi and the body fluid analagous to the interchange of calcium and phosphate between bone and plasma, the latter interchange governed by the parathyroid hormone. It may be noted that ACTH increases the uric acid excretion in the urine. In gout a fraction larger than normal of the dietary amino acids seems to be converted into uric acid, thus increasing the miscible pool, although not necessarily the serum uric acid. In birds and reptiles the bulk of urinary nitrogen is excreted in the form of uric acid (uricotelic excretion), whereas in man and most other species it is excreted in the form of urea (ureotelic excretion). Thus the metabolic defect in gout may be attributed to an abnormally large uricotelic component in a ureotelic species (Stetten).

## PATHOLOGICAL PIGMENTATION

The group of substances known as pigments have nothing in common save that they are colored, but it is convenient to consider them together. They may be produced within the body (endogenous pigments) or introduced from without (exogenous pigments). There are three chief groups of endogenous pigments: (1) melanins, (2) lipochromes, and (3) derivatives of hemoglobin. Pigment metabolism may become pathological owing either to overproduction or underproduction.

**Melanosis.**—Melanin, derived from the Greek *melas*, meaning black, is the coloring matter of the skin, hair, iris, choroid coat of the eye, and

certain parts of the central nervous system. The pigment is in the form of granules, which vary in color from light brown to black. Melanin is formed from the amino acid tyrosine by the action of the enzyme tyrosinase, a copper-protein complex. The presence of copper ions is necessary for the activity of the enzyme. Tyrosinase was demonstrated in mushrooms as long ago as 1896, and is known to be present in plants, insects and marine animals. Indeed it is found in greatest abundance in the cells lining the ink-sac of the cuttlefish. It was more than half a century later that Lerner and Fitzpatrick succeeded in showing that tyrosinase is also present in mammalian tissue, including human skin. This can be done by incubating sections of tissue in a buffered solution of tyrosine with acts as the substrate. The formation of melanin indicates the presence of tyrosinase.

A similar reaction, the dopa reaction, was introduced previously by Bloch. Dopa is a contraction for dihydroxyphenylalanine, an amino acid which reacts with tyrosinase to produce melanin. Tyrosinase has the ability to catalyze the oxidase of both tyrosine and dopa with the formation of melanin, but in normal mammalian skin the ability to catalyze tyrosine oxidase is absent or rather inhibited, while the ability to catalyze dopa is present. This is true also of the nevus, a benign tumor of melanin-forming cells. In malignant melanoma, the malignant variety of these cells, both tyrosine and dopa are catalyzed by tyrosinase.

The cells which form the pigment are peculiar branched cells derived from the neural crest and intercalated among the basal cells of the Malpighian layer of the skin. They may or may not contain pigment granules. These cells are known as melanocytes to the biologist, the person fundamentally concerned with the problems of pigment in the animal kingdom, but the pathologist calls them melanoblasts, a term reserved by the biologist for the immature pigment cell during its migration from the neural crest. A macrophage which takes up melanin discharged from the melanocytes is known to the biologist as a melanophage, to the pathologist as a melanophore (*phoreo*, I carry). The terminology of the biologist has been recommended for general use, but old names are hard to relinquish. Applying the dopa reaction to these various cells, it is obvious that the melanoblasts (melanocytes) and the tumor cells arising from them will be dopa-positive, while the melanophores will be dopa-negative.

*Inhibitors* of melanin formation demand brief consideration. The removal of copper ions and the action of ascorbic acid both inhibit tyrosinase. Copper is essential for the activation of the enzyme and for normal pigmentation in mammals. Copper-deficient diets result in depigmentation of the skin of the experimental animal. Sulphur-containing compounds, such as thiouracil, remove the copper by combining with it. Thiouracil administered to a black rat causes depigmentation, and in a patient with malignant melanoma and melanuria it has been known to change the urine from black to a normal color.

It would appear that in the skin of white persons sulphhydryl groups may bind the copper and inhibit activation of the tyrosinase, so that little or no melanin is formed even though tyrosin and tyrosinase are both present. Ultraviolet energy activates the system, probably by decreasing the concentration of the sulphhydryl groups, so that melanin appears in the melano-



blasts (melanocytes) and in their long dendritic processes. This is the mechanism of sun-tanning and serves to explain the melanosis of those living under a tropical sun. Temperature also influences the reaction, which is the probable reason why the pigmentation of Addison's disease is marked not only in those parts exposed to the light but also in creases and folds of the skin covered by clothes.

In man the normal amount of melanin in the skin is very small. It is much greater in the negro than in the white man, but even in the negro the entire skin does not contain more than one gram of pigment. In the malignant melanoma as much as 300 grams of melanin have been removed from the liver alone, so that under some conditions the pigment-forming power of the body is greatly increased. As the result of inflammation of the skin the melanin may become mobilized and transported by melanophages to the regional lymph nodes, where the microscopic picture may simulate that of a melanotic tumor.

In man the function of melanin appears to be to serve as a protection against strong actinic light. In cold-blooded vertebrates the behavior of pigment in response to stimuli is of much greater importance. This response consists in the dispersion of melanin granules in the long dendritic melanocytes, so that the pigment may seem to ebb and flow in the skin. Changes in temperature and environment and the use of certain drugs activate these changes in the frog and in fish, but only when the animal has an intact pituitary. It would appear that at least in the frog the pituitary controls the movement and possibly the production of melanin. A melanocyte stimulating hormone, MSH, has been obtained from the pituitary. When MSH is injected into the hypophysectomized frog it causes melanin dispersion, and even does so when incubated with a piece of isolated skin.

The part which MSH plays in the control of pigment movement has been proved in the frog, but not yet in man. A number of clinical facts suggest that in man also the pituitary may exercise an important influence over melanin. Conditions believed to be associated with increased pituitary activity, such as pregnancy, Addison's disease and acromegaly, often show a marked increase of melanin pigmentation. In the third trimester of pregnancy the serum copper is increased, MSH is present in the urine in large amount, and pigmentation of the skin occurs in areas exposed to sunlight, a triad to which the name of *melasma* has been applied. The same is true of Addison's disease, in which decreased adrenal cortical activity seems to be compensated for by overactivity of the pituitary and a great increase in the formation of melanin. The presence of MSH in the urine in pregnancy can be demonstrated by an increase of melanin in the frog's skin when the urine is applied topically. When the activity of the pituitary is decreased, as in panhypopituitarism, there is a disappearance of pigment from the skin. Copper seems to play a part in this mechanism. Administration of MSH causes the serum copper to rise, and this is accompanied by increase in melanin formation.

It is possible that the pigmentation of Addison's disease, in which both adrenals are destroyed, may be more directly dependent on adrenal hormones. If these control the concentration of sulphhydryl groups at the site of melanin formation, loss of the hormones would result in decrease of

sulphydryl concentration and the melanin-forming enzyme system would no longer be inhibited. Another suggestion depends on the fact that epinephrin and melanin are derived from the same precursor. If the adrenals do not use this substance for the manufacture of epinephrin, it may accumulate and be converted into melanin. It must be admitted, however, that the mechanism responsible for the pigmentation in Addison's disease is not yet fully understood.

Estrogenic hormones may also play a part in the control of pigmentation. Estrogens given orally induce pigmentation in the nipples and areolae in man, and local unilateral application to the nipple produces the same result in the guinea pig.

Under pathological conditions too much melanin may be formed or too little. The chief examples of too much pigmentation are the melanotic tumors, Addison's disease, melanosis coli, and chloasma. Ochronosis is related to melanosis. Diminished formation of melanin is seen in albinism and leucoderma. When too much melanin is formed it is excreted in the urine. In Addison's disease and melanotic tumors the kidneys often contain much melanin in the epithelial cells of the loop of Henle and the collecting tubules. Here, as in other positions, it may be necessary to differentiate between melanin and hemosiderin granules, both of which are yellowish brown when thinly distributed. Hemosiderin can be stained a bright blue with the Prussian blue reaction and melanin deep black by the Fontana silver technic.

For further information on the behavior of melanin in health and disease the excellent review by Lerner and Fitzpatrick should be consulted.

*Melanosis coli* is a condition in which a black pigment, either melanin or closely related to melanin, is deposited in the mucous membrane of the large intestine and appendix. Like so many other pathological states, it was first described by Virchow. The extreme grades are comparatively rare, but if the slighter forms are included the incidence is fairly high. Stewart and Hickman found it in 11.2 per cent of 600 autopsies. The incidence is higher in those over middle age, and much higher in carcinoma of the colon. Melanosis of the appendix may occur apart from any pigmentation of the colon; it may be seen in appendices removed at operation. The coloration which varies from gray to inky black can be seen through the intestinal wall, and is sharply limited by the ileocecal valve. In advanced cases there may be metastases of pigment to the submucosa and the mesocolic lymph nodes. The granules of pigment are found within large mononuclear cells in the stroma of the mucous membrane; the epithelium is not affected. The condition is often associated with chronic intestinal stasis either from organic obstruction or simple constipation. The pigmented cells are "dopa"-negative, and are, therefore, melanophores that have taken up pigment which has either been ingested in the food or synthesized in the bowel.

**OCHRONOSIS.**—This very rare condition was given its name by Virchow because of the ochre color which the nose and ears may present (*ochros*, sallow). There is a blackish discoloration of the cartilages, and sometimes of connective tissue, селе-  
rae, muscles, and epithelial cells. When the cartilages are subcutaneous (nose, ear), the color may shine through the skin. The pigment may be deposited in the kidneys. In the only case which I have seen, the pyramids of the kidneys and the choroid plexus of the lateral ventricles were a startling black color. The skin of this patient was a peculiar gray as if it had been black-leaded. The pigment is either

melanin or closely related to that substance. In the majority of the cases reported there has been marked alkaptonuria. In a few cases there has been prolonged use of carbolic acid dressings. It is supposed that the pigmentation is due to the action of tyrosinase on aromatic protein decomposition products (tyrosin, phenylalanine, etc.), or phenol derivatives in the carbolic acid cases.

Other examples of melanosis or pigmentation in which a melanin-like substance is formed can only be mentioned. *Chloasma* is a condition in which brown patches appear in the skin of the face and elsewhere. They are seen in pregnancy and diseases of the uterus and ovaries, tuberculosis, Graves' disease, and following the application of heat (hot-water bottles). In cachexia the skin often shows patches of pigmentation. If such a patch be excised it will be found to give a marked "dopa" reaction. The body louse injects a fluid which produces a black spot of melanin in the deepest layers of the epidermis. An emulsion of the insect's salivary glands has the same effect when injected.

*Absence of melanin* is much rarer than excess of the pigment. *Albinism* is a congenital absence of melanin, which may be partial or complete. In *leucoderma* there are white patches of skin, as the name implies, due usually to a process of depigmentation; a section of such a patch is negative to the "dopa" reaction, suggesting that the cells are lacking in the specific ferment. White patches of skin are found in leprosy, due apparently to interference with the nerve supply. The bleaching of hair is due to a loss of melanin. The white winter fur of arctic animals contains no melanin.

**Lipochromes.**—The colored fats form a loose group regarding which little is known. They are yellowish granules found in the heart muscle, nerve cells, seminal vesicles, adrenal cortex, corpus luteum, and interstitial cells of the testis. They have been called "wear and tear" pigments, being apparently produced from the cytoplasm in the process of wasting. The best example is *brown atrophy of the heart*, a wasting of the myocardial fibers seen in old age and cachectic disease conditions, and accompanied by a great collection of brown granules in the muscle fibers at either pole of the nucleus. These granules, which are normally present in small amount, stain red with Sudan. Similar granules are seen in the nerve cells, especially the large cells of the cerebral cortex, in senile and mental conditions. Some of these pigments may belong to the group of *plant pigments* (carotin and xanthophyll) found in carrots and other vegetables, egg-yolk, etc. If a person eats too many carrots he may develop *carotinemia*, with bright yellow coloration of the blood serum, the palms of the hands, and the nasolabial folds. The condition is sometimes seen in diabetes.

**Hematogenous Pigmentation.**—The red blood corpuscles are continually being destroyed in health. In disease this process may be greatly increased. The destruction may be local, as in a hemorrhage, or general as in hemolytic diseases. Hemoglobin contains iron, but does not give an iron reaction with the ordinary tests. When it is broken down two moieties are found: the one, hematoidin, is iron-free, while the other, hemosiderin, contains iron and gives the iron reaction. The iron-free portion is converted into bilirubin, and excreted in the bile, but the iron of the hemosiderin is too valuable to be lost and is retained within the body to be built up again into hemoglobin.

*Hematoidin.*—Hematoidin may assume the form of brown rhombic crystals or of amorphous granules seen in the neighborhood of any old

hemorrhage. The granules are usually extracellular, but may also be found within phagocytic cells. Hematoidin is identical with bilirubin, and is excreted as such in the bile. In conditions of increased hemolysis there is therefore an increased formation of bilirubin; this may accumulate in the blood and stain the tissues yellow, giving rise to that form of jaundice known as hemolytic jaundice. When the van den Bergh test for bilirubin is applied to local and not too recent extravasations of blood, a positive reaction is obtained. It is only when the hemorrhage is large and absorption is imperfect that the pigment is deposited in solid form. In small hemorrhages the pigments are soluble and stain the surrounding tissue with the familiar color of a bruise.

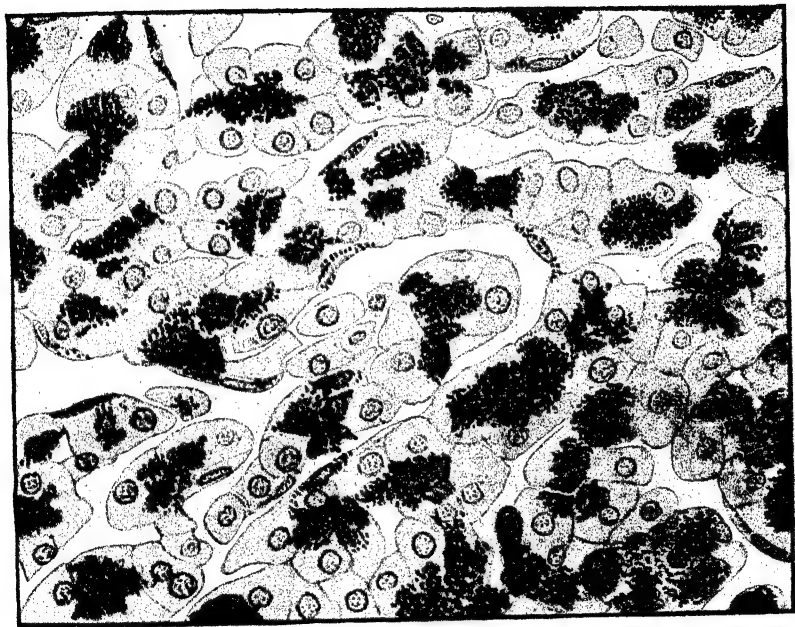
*Hemosiderin*.—Hemosiderin, the iron-containing pigment, gives the Prussian blue reaction for iron with potassium ferrocyanide and hydrochloric acid. This test may be applied either to microscopic sections or to the gross specimen. The pigment takes the form of fine yellowish-brown crystals which are usually contained within cells. Hemosiderin, therefore, is chiefly intracellular, hematoidin chiefly extracellular. The hemosiderin may be formed as the result of hemorrhage or of general hemolysis. In the former the hemosiderosis is local, in the latter it is widespread. The reticulo-endothelial system is intimately connected with hemosiderosis in three different ways: (1) The pigment-filled cells which surround an old hemorrhage are histiocytes belonging to this group. (2) Certain hemolytic diseases, *e. g.*, hemolytic jaundice, are dependent on the activity of the reticulo-endothelial system; the hemolysis is followed by the deposition of hemosiderin. (3) General hemolysis may be due to some extraneous source such as snake venom, but again hemosiderin is found within the reticulo-endothelial cells.

Hemolysis from whatever cause is therefore likely to be followed by hemosiderosis. The pigment is not only found in the reticulo-endothelial cells, but also in the epithelial cells of the liver and kidney. A marked Prussian blue reaction is obtained in those cells in pernicious anemia. Hemolysis is always accompanied by an increased formation of bilirubin. When this is marked it can readily be detected in the blood; it stains the tissues, but does not escape in the urine. In the curious condition of paroxysmal hemoglobinuria there is marked hemosiderosis of the liver and the cells of the convoluted tubules of the kidney as the result of the increased destruction of blood.

There may be an increase in the iron content of certain tissues, and yet the iron may not be demonstrable by ordinary histological methods. This invisible iron can now be demonstrated microscopically (Popoff). It is readily detached from the erythrocytes, and is rapidly taken up by mesenchymal and epithelial cells. Siderosis due to this cause is seen in hemolytic and other conditions, but it is especially striking in congestive heart failure, in which practically all the septal cells of the lung may be seen to be loaded with iron granules instead of a mere sprinkling of phagocytes containing hemosiderin.

**MALARIAL PIGMENTATION.**—The malaria parasite within the red blood cells forms a dark brown pigment which is liberated with the destruction of the red cells

## PLATE II



Liver Showing Hemochromatosis.

Prussian-blue reaction for iron. The hemosiderin granules are present mainly in the liver cells and to a lesser degree in the Kupffer cells.

and deposited in large quantities in the spleen and liver. This pigment does not give the Prussian blue reaction and at one time it was believed to be melanin, but it contains iron. Hemosiderin may also be deposited in addition to the malarial pigment.

**HEMOCHROMATOSIS.**—This rare disease, also called *bronzed diabetes*, is a disorder of iron metabolism, but its exact nature is still a mystery. The normal amount of iron in the body is only 2.5 grams, but in this disease the liver alone may contain 30 grams or more. (Plate II.) The pancreas also contains large amounts of iron. Smaller quantities are found in the kidneys, adrenals, spleen, heart and voluntary muscles, thyroid, skin, and lymph nodes in the upper abdomen. The organs containing the pigment have a brown color (hence the name of the disease), and the skin may be bronzed (bronzed diabetes), although this is uncommon. The pigmentation of the skin is due to melanin, not to iron, so that it is useless to do a biopsy in order to test the skin for iron. The affected organs give a vivid Prussian blue reaction.

One of the great problems is the source of the iron pigment. The probable explanation is that there is some fundamental defect in iron metabolism. Sheldon, whose splendid monograph should be consulted, is of the opinion that this defect is inborn and inherited. It has been suggested that there is an overabsorption of iron by the intestinal mucosa. Normally very little iron is excreted, so that if too much is absorbed it may accumulate in the body for years. In support of this idea it has been found that repeated bleeding by venesection has reduced the iron content of the liver as shown by biopsy, and has led to marked subjective improvement. Despite the name there is no evidence to indicate that the iron is derived from the blood by hemolysis. The work of Gillman and Gillman indicates that at least in some cases the disturbance may be nutritional in origin. These workers, in an investigation of the deficiency disease pellagra in South African negroes by means of repeated liver puncture, were able to demonstrate a series of changes in the liver cells beginning with fatty degeneration and ending with massive accumulations of iron identical with those seen in hemochromatosis. They believe that in their clinical material one of the commonest sequels of pellagra is hemochromatosis. The iron appeared to develop in or from the mitochondria of the liver cells. The condition should be called cytosiderosis rather than hemochromatosis. In addition to the iron pigment there is another pigment known as hemofuscin which does not give the iron reaction with Perles' stain. Gillman and Gillman believe this to be lipoidal in character, and suggest the preferable name cytolipochrome. It also appears to be derived from breakdown of the mitochondria.

The liver cells slowly undergo necrosis, and marked cirrhosis may develop, which constitutes one of the most serious features of the disease. Primary carcinoma of the liver develops in about 20 per cent of cases. In the pancreas destruction of the islets of Langerhans as well as of the acinar tissue takes place, and glycosuria develops (bronzed diabetes).

**SIDEROSIS OF THE GLOBUS PALLIDUS.**—The globus pallidus of the lenticular nucleus usually gives a marked iron reaction, due to the presence of iron in the walls of the vessels in this region of the brain. The condition has been mistaken by many workers for calcification owing to the dark blue staining with hematoxylin. (Fig. 12.) The walls of the vessels are infiltrated with iron salts which appear to be derived from the nucleus itself. The iron is seemingly not hematogenous in origin, and there is no increase in conditions of undue hemolysis. Hadfield considers that pallidal siderosis is the expression of a slow involutionary atrophy affecting the lenticular nucleus in at least 60 per cent of persons over the age of thirty years. It appears to predispose to the acute bilateral necrosis of the lenticular nuclei which is so often seen in carbon monoxide poisoning.

**BILIARY PIGMENTATION.**—The subject of jaundice is considered in detail in the section on the liver. The pigments of the bile are formed from the blood. When red blood cells are broken down either in health or as the result of disease, hematin is formed which is identical with bilirubin. The bilirubin is formed not by the epithelial cells of the liver, but by the reticulo-endothelial cells in the liver (Kupffer cells) and throughout the body. The hepatic cells merely excrete the pigment, passing it from the blood into the bile ducts. If bilirubin accumulates in the blood the tissues become stained. The skin and whites of the eyes appear yellow, and the patient is said to be jaundiced. It is evident that bilirubin may accumulate in the blood for two reasons: (1) It may not be excreted owing either to an obstruction in the course of the bile passages or to sickness on the part of the liver cells; (2) it may be produced in excessive amount owing to undue hemolysis. The former is called obstructive jaundice, the latter hemolytic jaundice.



FIG. 12.—Iron in vessel wall in lenticular nucleus.  $\times 150$ .

For a few days after birth the bilirubin of the blood is always above normal, and definite jaundice may develop. This is known as *icterus neonatorum*, and the bilirubin is hemolytic in type. The newborn child has a polycythemia, because the fetus lives in a constant condition of oxygen want and therefore needs a greater number of red blood cells to carry the oxygen to the tissues. After birth many of these cells are no longer needed and are broken down with the formation of bilirubin. The pigment may be deposited in the form of needle-like or rhombic crystals of hematin in the pyramids both in the collecting tubules and the interstitial tissue; these masses of pigment are called *bilirubin infarcts*.

**Exogenous Pigmentation.**—Pigments may be introduced from without and be deposited in the body. This introduction may occur through the respiratory tract, the alimentary canal, and the skin.

Through the *respiratory tract* dusts may be inhaled and deposited in the lungs, where they cause varying degrees of chronic irritation, a condition known as pneumokoniosis. Of these dusts the only two of importance are silica (in gold miners and stone masons) causing silicosis, and coal dust (in coal miners) causing anthracosis. These diseases are considered in the section on the Lungs.

*Alimentary canal* pigmentation is of much less importance. The two most important examples are silver and lead. Long-continued administration of silver salts may give rise to a condition of *argyria*. The silver is deposited as an insoluble albuminate in the form of fine granules. The skin and conjunctiva may assume an ashen-gray color, and there is pigmentation of the internal organs. The pigment causes no disturbance, but the importance of the condition lies in the fact that the coloration of the skin is permanent, so that the face has an ashen appearance for

the rest of the patient's life. The pigment is not intracellular, but seems to lie in the cement substance. In the skin it is found in the corium just under the epithelium and around the sweat and sebaceous glands. In the kidney it is chiefly in the glomeruli and outside the epithelium of the tubules. In other organs the distribution is similar.

Lead poisoning or *plumbism* is considered in the section on the Action of Poisons. Pigmentation of the gums is a common sign. The lead is absorbed from the alimentary canal or may pass through the skin. It circulates in the form of a soluble salt, and when this comes in contact with hydrogen sulphide formed from decomposing food around diseased teeth, lead sulphide is formed and deposited in the gum where it gives a characteristic "blue line."

Pigment is introduced through *the skin* in the process of tattooing. It is taken up by histiocytes and is lodged permanently in the connective-tissue spaces. None is found in the epithelium. Some of the pigment is carried by phagocytes to the lymph nodes where it is deposited.

## DISORDERS OF CALCIUM METABOLISM. CALCIFICATION

The occurrence of pathological calcification, the deposition of calcium salts in tissues other than bone, has been known for centuries, but during the last few years a flood of light has been thrown on general disturbances of calcium metabolism and on a number of diseases in particular. Calcium is one of the elements which is essential to life. The average blood calcium in health is 10 mg. per 100 cc. of blood and remains remarkably constant. Salts of calcium are deposited in the tissues: (1) In the normal process known as the ossification of bone; (2) in the pathological process known as calcification. The composition of the calcareous deposits in both processes is extraordinarily similar, there being about 9 parts of calcium phosphate to 1 part of calcium carbonate. In *ossification* the salts are deposited diffusely in specially prepared osteoid tissue which has a definite architecture and the cells of which exercise a controlling influence on the process so that they are called osteoblasts. In *calcification* the same salts are deposited as clumps of granules in tissue which is either dying or dead and from which all cells have disappeared. In both the proportion of carbonate to phosphate is so constant that it would appear as if a calcium carbonate-phosphate complex is first formed from which the individual salts are precipitated.

Several diseases are associated with a disturbance in calcium metabolism, mostly in the nature of a hypocalcemia. Rickets and osteomalacia will be discussed in relation to diseases of bone, and so need only be mentioned here. In *rickets* there is a serious disturbance of the normal process of ossification in the growing bones of children, accompanied by other disturbances and dependent on a deficiency of calcium or phosphate or vitamin D in the diet. It can be cured by the administration of vitamin D in the form of cod-liver oil or by ultra-violet light, the action of which on the ergosterol of the skin serves to convert it into vitamin D. *Osteomalacia* is a disease of adults characterized by marked decalcification and softening of the skeleton followed by the development of bone deformities. This also appears to be a deficiency disease, and may be regarded as an adult form of rickets. The parathyroids may be enlarged, but this appears to be a compensatory hyperplasia and not the cause of the osteomalacia as is



believed by many. *Tumors of the parathyroids* may cause marked decalcification of the bones, a condition known as *osteitis fibrosa cystica*. The effect of these parathyroid tumors is very remarkable. The blood is flooded with calcium, but much of it is excreted in the urine. The calcium removed from the bones may be deposited in the kidney to form renal calculi or in the walls of the arteries. A curious feature is the development of tumor-like swellings in connection with the bones, giving the microscopic picture of giant cell tumor of bone. These matters are discussed in detail in Chapter 32. *Tetany* is a manifestation of calcium deficiency characterized by a hyperexcitability of the nerve-muscle system. An excess of calcium ions or of hydrogen ions tends to depress this system, while a deficiency in these ions leads to hyperexcitability. Tetany may be induced by anything which lowers unduly the blood calcium by parathyroid deficiency, rickets, over-ventilation of the lungs (with undue loss of carbon dioxide), pyloric stenosis (with undue loss of hydrochloric acid by continuous vomiting), or by feeding large amounts of sodium bicarbonate—in a word, by anything which leads to a low blood calcium or tissue alkalosis. The presence of calcium is necessary for the clotting of blood.

**Calcification.**—Pathological calcification may occur as the result of the blood being flooded with calcium. This may be induced by repeated injections of parathyroid extract, or it may occur in such decalcifying diseases as osteomalacia, general carcinomatosis of bone, and multiple myeloma. The calcium is removed from the bones and deposited in other tissues. This variety is therefore known as *metastatic calcification*. The lime is deposited chiefly in the lungs, kidneys, and the mucous membrane of the stomach, probably in the living cells. The reason for the deposition is the hypercalcemia, not any degeneration on the part of the tissues involved. Enormous single doses of irradiated ergosterol (vitamin D) will produce massive calcification in the aorta, coronary arteries and heart muscle of the rat in forty-eight hours (Ham). At the end of twenty-four hours there is no indication in the tissues that a catastrophe is imminent, so that the chief factor in this case seems to be the inability of the serum to retain the calcium salts rather than degeneration on the part of the tissues.

It is much more common for the calcium to be laid down in dying or dead tissue without any reference to the blood calcium. Both phosphate and carbonate are deposited in practically the same proportion as is found in bone. The salts are soluble in weak acids, bubbles of carbon dioxide being given off owing to the presence of carbonates. The lime is stained blue with hematoxylin and black with silver nitrate. The mechanism by which the calcification occurs has long been a matter of dispute. According to Klotz there is first fatty degeneration; the fat is hydrolyzed with the liberation of a fatty acid; the calcium unites with the fatty acid to form a calcium soap; the fatty acid is then replaced by the carbonic acid and phosphoric acid in the blood, and the final result is calcium carbonate and calcium phosphate. Wells fails to find any evidence of the formation of a soap, and regards the process as a physical rather than a chemical one, the calcium and phosphate being absorbed by the degenerated tissue. He found that pieces of sterilized cartilage placed in the peritoneal cavity of a rabbit soon became calcified, having taken up the lime from the fluid in

which they were bathed. It is probable that there is truth in both views. The areas of fat necrosis which result from acute pancreatitis may show striking calcification, and the same change may occur in a degenerating lipoma. In these cases it seems likely that Klotz's view is correct. There is, however, a tendency for any dying or dead tissue surrounded by living tissue and accessible to the body fluids to become calcified. In such necrotic areas circulation is absent, but a slow diffusion takes place from the surrounding blood and lymph. The dying tissue undergoes a hyaline change, and it is this hyaline material in which the carbon dioxide tension is probably low owing to tissue inactivity that becomes the seat of calcification. Necrosis and hyaline changes are the two chief antecedents of calcification. The physical rather than the chemical structure, as Wells remarks, seems to determine the deposition of the calcium.

Endless examples of calcification could be given, but a few will suffice. *Caseous tuberculous areas*, especially in the lungs and lymph nodes, frequently become calcified. The change usually indicates that the infection has died out and healing has occurred. In one form of *arteriosclerosis* (atheroma) the intima of the vessel develops calcareous patches (here preceded by fatty changes); in another form the media of the arteries to the limbs is affected. *Valves of the heart* which have been injured by previous inflammation are often calcified. Lime salts are often deposited in an *old abscess* in which the pus has become inspissated. A long-standing *empyema* or *pericarditis* may undergo the same change, so that calcareous patches are formed over the lung or the heart. A *thrombus* in a vessel may be calcified; such stony nodules, known as *phleboliths*, are often detected in the pelvic veins in roentgen-ray films. *Degenerating tumors*, especially fibroid tumors of the uterus, may become converted into masses of stone. In old age the *cartilages of the ribs* and the trachea are often calcified. A fetus which escapes into the abdominal cavity from a tubal pregnancy may become a *lithopedion*, a calcified fetus. A coating of lime may be formed over *animal parasites* in the tissues, particularly *Trichina spiralis* and *echinococcus* cysts. *Dead ganglion cells* in the brain may become encrusted with lime, so that a perfect cast of each cell may be formed. A peculiar example which deserves special mention is the calcification of the *convoluted tubules of the kidney* which rapidly develops after corrosive sublimate poisoning; here the calcium is deposited in the necrotic cells. It may be noted that even brief obstruction of the renal artery in the rabbit is followed by extensive calcification of the kidney.

## NECROSIS

By necrosis is meant the local death of cells. Now although death may be regarded as the final degeneration, a cell which has been suddenly killed shows no sign of degeneration. It looks exactly like a normal one. This after all is natural, for the fixed cells of microscopic sections have all been killed. The cellular changes characteristic of necrosis are changes which the cell undergoes *after* it has died while still remaining in the body. These changes are very similar to those undergone by living cells when they are removed from the body and allowed to die, being due to the same cause,

namely, the action of enzymes. It is evident that necrotic changes may easily be confused with those of postmortem degeneration, and the distinction is sometimes hard to make. The term *necrobiosis* is used to indicate the gradual degeneration and death of a cell, but it appears to be somewhat superfluous.

**Causes.**—1. *Loss of Blood Supply.*—When the supply of oxygen and food is cut off, the cells of the part rapidly undergo necrosis. This is well seen in an infarct caused by blockage of a vessel by a blood clot. Even though the cutting-off of the blood is only transient, the cells may be killed. The time necessary varies with the tissue; the secreting cells of the kidney may be killed while the connective tissue survives. Thrombosis of the vessels to a part is followed by necrosis unless a collateral circulation can be quickly established.

2. *Bacterial Toxins.*—The action of toxins is the commonest cause of necrosis. The reader can supply examples for himself. As the toxins act on the vessels of the part and are apt to produce thrombosis, it is evident that the first two causes are often combined. Much depends on the concentration of the toxin; if the toxin is weak inflammation is produced; if strong the result is necrosis.

3. *Physical and Chemical Agents.*—The various physical and chemical irritants which may produce inflammation may also lead to necrosis. Heat is much more injurious than cold. Heat above 45° C. will kill cells, whereas freezing may leave them unaffected. The death of tissue following frostbite is due to injury to the vessels and thrombosis rather than to any direct action on the cells. Electricity, roentgen-rays, and radium rapidly cause cell death if in sufficient concentration. Caustics and other poisons, trauma, and continued pressure may produce the same result.

**Structural Changes.**—Necrosis can be recognized by changes in the cell body and in the nucleus. The *cellular changes* are swelling of the cytoplasm which becomes homogeneous and loses its normal reticulated appearance. There is loss of the normal sharp contour and obliteration of the cell boundaries. Muscle fibers lose their striations and become swollen and homogeneous. *Zenker's degeneration*, which is best seen in the rectus abdominis and diaphragm in typhoid fever, is an example of necrosis with hyaline changes. The *nuclear changes* are even more striking, and should be looked for in determining the presence of necrosis. There are three possible changes. (Figs. 13 to 15.) (1) *Chromatolysis* or *karyolysis*, in which the nuclear chromatin appears to be dissolved and the nucleus gradually fades from sight. This is the commonest change. (2) *Karyorrhexis*, in which the nucleus is broken up into a number of small fragments, well seen at the edge of an infarct. (3) *Pyknosis*, in which the nuclear material is condensed into a small deeply-staining mass. The student must learn to recognize necrosis under the microscope, because he will encounter tissue death in most diseases and in every organ of the body.

The gross appearance also varies, there being two main types known as coagulation necrosis and liquefaction or colliquative necrosis.

**Coagulation Necrosis.**—Coagulation necrosis is the common form, and is characteristically seen in infarcts of the kidney or spleen. The part becomes dry, homogeneous, and opaque. There is coagulation of the cytoplasm

by intracellular enzymes. Perhaps some of the surrounding lymph may be absorbed and coagulated in the same way. The process is similar to coagulation of the blood. Architectural outlines (glomeruli, tubules) may be preserved though all cellular detail is lost. The coagulated material may remain unchanged for long periods of time, but at the margin of the infarcted area there is a gradual process of absorption owing to the action of proteolytic enzymes in the leucocytes brought by the circulating blood. In the course of time calcification may occur.

*Liquefaction Necrosis.*—Liquefaction necrosis occurs in the central nervous system. The necrotic area becomes softened and liquefied, and the fluid material is absorbed leaving a cyst-like space. The change is probably in some way dependent on the high lipid content of the nervous tissue.



FIG. 13



FIG. 14



FIG. 15

FIGS. 13 to 15.—Forms of nuclear degeneration in the tubules of the kidney.

FIG. 13.—Chromotolysis. The nuclei of the upper tubule have disappeared.

FIG. 14.—Karyorrhexis. The nuclei are broken up into small fragments.

FIG. 15.—Pyknosis. The nuclear material is collected into small compact masses.  
 × 500.

**CASEATION.**—Caseation is a form of necrosis in which all details of structure are wiped out, with the production of a dry, cheesy, granular material, completely amorphous. In ordinary necrosis, on the other hand, though the cells are destroyed the stroma is spared, so that the architecture is preserved. Caseation is the characteristic necrotic change of tuberculosis and syphilis. Tuberculous caseous tissue is not chemotactic, so that it attracts no leucocytes; the material therefore remains unchanged owing to the absence of leucocytic ferments. If secondary infection occurs there is invasion of leucocytes and softening may rapidly follow. Caseous material has a high fat content, and calcification is a frequent sequel.

**AUTOLYSIS.**—Autolysis plays an important part in producing the picture of necrosis. Take two pieces of fresh tissue, heat one for an hour at 55° C.

or boil it for a few minutes, then insert both pieces in the abdominal cavity of an animal. The fate of the two pieces will be very different. The heated piece in which the enzymes have been destroyed will undergo little change, the nuclei staining well after a lapse of months. The unheated piece will pass through the usual changes characteristic of necrosis owing to the autolytic action of its enzymes. If the two pieces are placed in normal saline and incubated, the heated piece will show no change, but the cells of the unheated piece will undergo enormous swelling due to the enzymes breaking down the large molecules into a greater number of small molecules

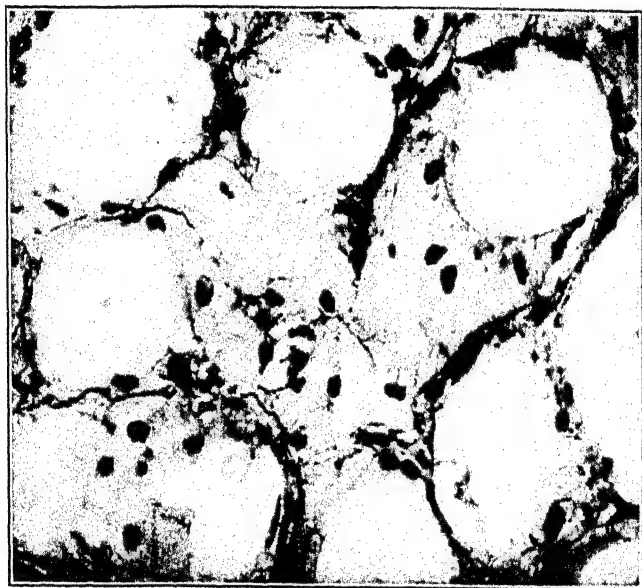


FIG. 16.—Fat necrosis. The necrotic fat cells have a cloudy appearance.  $\times 400$ .

with increase of the osmotic pressure and imbibition of fluid. For this reason dead cells floating in a fluid medium become very swollen. Autolysis proceeds much more quickly outside the body than in necrotic areas such as infarcts, because the plasma contains substances which inhibit the action of the enzymes.

**Fat Necrosis.**—When the pancreatic secretion is liberated in the abdomen owing to inflammation (acute pancreatitis) or injury to the pancreas, the fat-splitting ferment, lipase, acts upon the fat on the surface of the pancreas and in the omentum with the production of small opaque white areas of fat necrosis. The fat is split into glycerin and a fatty acid. The former is absorbed, while the latter remains in the cells as acicular crystals. The necrotic fat cells are easily recognized, because the material which they contain is much less soluble than normal fat, and is therefore not dissolved away in paraffin sections, giving the cells a cloudy appearance. (Fig. 16.) The patches may be rapidly removed; in experimental fat necrosis they have disappeared in eleven days. Calcium may unite with the fatty acid

to form a calcium soap, and lime salts may be deposited in the patches of necrosis rendering them permanent. Recent patches are surrounded by a zone of leucocytes. Owing to postmortem changes in the pancreas lipase may be liberated after death and produce fat necrosis. These postmortem patches can be distinguished from those produced during life as the result of disease by the absence of the zone of leucocytes.

*Traumatic fat necrosis* is quite a different matter. As a result of injury the fat cells of subcutaneous tissue may be injured, and an area of induration partly necrotic, partly inflammatory in character, is produced. The fat cells resemble those in the opaque patches of pancreatic fat necrosis, containing insoluble material in paraffin sections. A well-marked inflammatory reaction is seen around and within the affected area; foreign body giant cells often form a striking feature so that the lesion may be mistaken for tuberculosis or syphilis. The breast is the most common site.

## GANGRENE

Gangrene is death of a part with putrefaction superadded.

The essence of the process is putrefaction. In the student's mind and in that of the surgeon there is often confusion as to the difference between gangrene, necrosis and infarction. In gangrene the tissues become putrid and rotten owing to the action of saprophytic putrefying bacteria. Necrosis is a microscopic term indicating cellular death, whilst infarction is a gross term signifying death of a part owing to sudden ischemia. An infarct is of course necrotic, but bacteria play no part in the process.

Saprophytes grow only in dead tissue, so that gangrene can only occur in parts which are already dead and which are exposed to these bacteria. It is therefore found in skin surfaces, and in the mouth, bowel, lung, cervix, etc. It does not occur in the heart, liver or spleen. Gangrene may be moist (wet) or dry. In moist gangrene there is abundant fluid in the part due to venous obstruction, lack of evaporation, etc., a condition which favors the prolific growth of putrefying bacteria. It therefore occurs in internal organs (bowel, lung), or in an extremity when veins as well as arteries are occluded. Dry gangrene occurs where there is little fluid in the tissues owing to evaporation or good venous drainage. It is therefore confined to the extremities and is caused most characteristically by the gradual narrowing of the lumen of an artery by arteriosclerosis, so that the tissues have time to become dried out. Sudden obstruction of an artery by an embolus may lead to moist gangrene. A common belief is that bacterial infection plays no part in dry gangrene. This is a mistake. The classical color change of the part (see below) is due to the action of saprophytes on the blood, and these bacteria can be demonstrated if the part is incubated in a fluid medium.

**Dry Gangrene.**—Dry gangrene is seen in typical form when the arteries to the foot are closed off in old age as the result of arteriosclerosis. The part is cold and pulseless, there is no collateral circulation, and with or without a slight injury gangrene begins in one of the toes, as these are farthest from the blood supply. The part contains so little blood that invading bacteria grow with difficulty in the dead tissue, and the spread of

the gangrene is slow. The part becomes dry, shrivelled and dark like the foot of a mummy. Hemolysis of the red blood cells liberates the hemoglobin, which is acted on by the hydrogen disulphide produced by the bacteria with the formation of black sulphide of iron so that the tissues are stained black. The gangrene extends slowly upward until it reaches a point where the circulation is sufficient to keep the part alive. At this level a line of separation is formed between the living and dead tissue. The line consists of inflammatory granulation tissue, which erodes the dead tissue and finally brings about complete separation. The microscopic picture is one of complete necrosis, but in addition there is usually a blurring and smudging of outline, a disintegration and breaking-up of tissue beyond what is seen in simple necrosis.

**Moist Gangrene.**—Moist gangrene is the same process in a part containing fluid, but the effect on the patient is very different. Gangrene of internal organs (lung, bowel, etc.) is always of the moist variety. It rapidly develops when the venous as well as the arterial flow is blocked and the part becomes filled with blood. This is seen in the limbs (injury to a main artery and vein) as well as in the viscera (strangulated hernia). It may also develop in naturally moist external regions (vulva). The tissue becomes rotten and putrid, in sharp contrast to the necrosis of such a lesion as an infarct. Owing to the abundant moisture there is rapid growth of putrefactive bacteria which break down the dead tissue with the formation of foul-smelling nitrogenous end-products such as indol and skatol. The organisms cause liquefaction of the tissues and sometimes gas formation, so that blebs of fluid form under the skin and bubbles of gas give an emphysematous crackling when the part is palpated. Sulphide of iron is formed from the decomposed hemoglobin as in dry gangrene, and the parts are stained dark blue, green, and black. The local spread of the condition is very rapid and there is no attempt to form a line of demarcation. The most serious feature is the great absorption of toxic products which cause profound toxemia and finally death. In dry gangrene little or no absorption takes place.

**Causes.**—The two great factors are loss of blood supply and bacterial infection; often these two are combined. *Senile gangrene* occurs in old people with arteries narrowed by arteriosclerosis, but the thrombosis is often responsible for the final occlusion. The gangrene begins in the foot, commonly in the big toe, and is naturally of the dry variety. *Diabetic gangrene* is very similar in type, though occurring in younger persons. Here again the arteries are narrowed, but in addition the sugar in the tissues favors bacterial growth. *Thromboangiitis obliterans* is often complicated by dry gangrene, usually in the lower limb but occasionally in the upper limb. The spasmodic narrowing of the arterioles in *Raynaud's disease* and in chronic *ergot poisoning* may lead to dry gangrene of the extremities. Sudden occlusion of an artery by *embolism* or *thrombosis* may result in gangrene, but only if the collateral circulation is insufficient for the needs of the part. In a limb with healthy vessels there is no danger of gangrene, but embolism of the superior mesenteric artery is certain to be followed by moist gangrene. *Inflammation* may be complicated by gangrene, especially when the vessels become thrombosed. Gangrene of an inflamed appendix is a good example

*Frostbite* may cause gangrene of such extremities as the fingers, toes, nose and ears. Necrosis is first produced by thrombosis in the vessels, and infection is superadded. Bedsores are an example of gangrene due to pressure which occludes the vessels leading to necrosis in a previously devitalized part. *Escharotics* (strong acids and alkalis) kill the tissues by direct action. Acids produce dry gangrene as they coagulate the fluids in the tissues; alkalis produce moist gangrene as they cause liquefaction of the tissue. *Carbolic acid* applications to a finger may be followed by death and gangrene in the course of a few hours.

*Gas gangrene* merits separate consideration. It is one of the most important complications of war wounds, and is occasionally seen after wounds in civil life and following surgical operations. The tissue is killed by trauma or the action of pathogenic bacteria. The dead tissue is then decomposed by saprophytic anaërobic bacilli with the formation of foul-smelling gas and fluid. The chief of these anaërobes are: (1) *Bacillus welchii* (*Bacillus aërogenes capsulatus*), (2) *Vibrio septique* (probably identical with the bacillus of malignant edema), and (3) *Bacillus oedematiens*. The gangrene, which is of the moist variety, affects principally the muscles. Gas can be pressed up and down the fibers, and softening and liquefaction soon follow. Microscopically the sarcolemma is seen to be separated from the fiber by a space filled with toxic fluid, so that the fiber loses its blood supply and quickly dies. As this fluid passes up and down the entire length of the fibers, the spread of the condition is very rapid.

## POSTMORTEM CHANGES

The changes which the body undergoes after death are of great importance. Without a knowledge of these it is possible to make grave errors in performing an autopsy by mistaking the results of these changes for the lesions of disease produced during life. They are also of great importance in medico-legal work in determining how long a body has been dead. The changes unfortunately depend on a number of variable factors, of which the most important are the temperature of the air, the temperature of the body at the time of death, and the presence of widespread bacterial infection. In spite of what one reads in detective stories it is seldom possible to fix the hour of death with any exactness. The two principal changes are rigor mortis and postmortem decomposition.

**Rigor Mortis.**—After death there is a stiffening of the muscles, a condition of rigor. It begins in the muscles of the face and passes downward until the legs are involved. It passes off in the same order. The time of onset as a rule is from one to six hours, and the rigor passes off in from one to two days. These times and the order in which the muscles are involved are of evident importance in medico-legal cases, but the times vary greatly. In persons dying in the midst of severe muscular exertion rigor mortis comes on so quickly that the body may become stiff almost at once. This sudden rigor is seen in soldiers killed in battle and in animals killed during the chase, and is due to the large amount of lactic acid in the muscles. In strychnine poisoning and in tetanus the stiffening is also sudden and very marked. On the other hand it is delayed, slight or absent in wasting dis-



cases, cachexia, starvation, etc. Rigor mortis is merely a coagulation of the muscle proteins to form myosin or muscle clot, and may be compared with coagulation necrosis. Its subsequent disappearance is due to the softening of the clot by autolytic enzymes. The muscle clot can be broken down by force so that the limb can be freely moved. Once the rigor is destroyed it does not return.

**Postmortem Decomposition.**—Decomposition of the body causes two main changes: (1) discoloration, and (2) softening. *Discoloration* is due to blood pigments and their derivatives. The red blood cells are hemolyzed after death, and the hemoglobin stains the vessel walls and the surrounding tissues. This is most marked in septicemia due to hemolytic bacteria, but in these cases some of the pink staining of the lining of the large vessels

may have been antemortem. With the onset of putrefaction sulphuretted hydrogen is formed in the intestinal canal and combines with the iron of the breaking-down hemoglobin to form black sulphide of iron which stains the tissues green and black. The color is first seen in the skin of the abdominal wall and on the surface of the abdominal organs.

*Postmortem softening* is due to the action of ferments, partly autolytic ferments in the tissues, partly the proteolytic ferments of the saprophytic bacteria causing putrefaction. The process is similar to that which occurs in moist gangrene. As the result of this ferment action the tissues are first softened and finally liquefied. This *postmortem digestion* may thin the stomach wall and cause actual perforation, so that the stomach contents are found



FIG. 17.—Foamy liver. Gross specimen showing the vacuolated appearance.

in the abdominal cavity. The hole in the stomach wall must not be mistaken for an antemortem lesion, traumatic or otherwise. The distinction is made by microscopic examination of the edge of the opening; in the postmortem lesion there is no inflammatory reaction. Softening of the pancreas may also occur, and the pancreatic juice may escape and produce areas of fat necrosis, but these also show no leucocytic reaction. The change proceeds very rapidly in hot weather, and when death has been due to some septicemic condition invasion of the body by putrefactive bacteria may occur even before death. When bacteria are found in the tissues at autopsy it must be realized that this may be merely a terminal invasion with no causal relation to the disease from which the patient died. Gas may be formed by the anaërobic saprophytes as in gas gangrene, and the liver may be full of bubbles like a sponge, a condition known as *foamy liver*. (Fig. 17.) When a body is kept in cold storage autolysis and bacter-

ial growth are greatly delayed, and when it is injected with chemical poisons as in the process of embalming, both ferments and bacteria are destroyed, and the tissues are preserved for long periods. In the kidney of an embalmed body which had been buried for nine months I found that the red blood cells stained perfectly and showed no evidence of hemolysis. The fixation of tissues for microscopic examination depends on the same principle of destroying autolytic ferments and bacteria as quickly as possible.

## ADDITIONAL READING

- Amyloid Degeneration.** BOOKMAN AND ROSENTHAL: *Am. J. Med. Sci.*, 1927, **173**, 396. JAFFÈ: *Arch. Path.*, 1926, **2**, 149. KUCYNSKI: *Klin. Wehnschr.*, 1923, **2**, 727. NOBEL AND MAJOR: *Arch. Path.*, 1929, **8**, 762. PAIGE: *Am. J. Path.*, 1931, **7**, 691. SMETANA: *Bull. Johns Hopkins Hosp.*, 1925, **37**, 383. TEILUM: *Ann. Rheum. Dis.*, 1952, **11**, 119.
- Calcification.** CAMERON: *Canad. Med. Assn. J.*, 1926, **16**, 753. HAM: *Arch. Path.*, 1932, **14**, 613. THOMSON AND COLLIP: *Physiol. Rev.*, 1932, **12**, 309.
- Cholesterol.** MULLER: *Medicine*, 1930, **9**, 119.
- Fatty Degeneration.** BELL: *J. Path. and Bact.*, 1914, **19**, 105. DIBLE: *J. Path. and Bact.*, 1932, **35**, 451; 1934, **39**, 197. DIBLE AND GERRARD: *J. Path. and Bact.*, 1938, **46**, 77. GOVAN: *J. Path. and Bact.*, 1943, **55**, 351. POPJÁK: *J. Path. and Bact.*, 1945, **57**, 87.
- Gas Gangrene.** MCNEE AND DUNN: *Brit. Med. J.*, 1917, **1**, 727.
- General Reference.** WELLS: *Chemical Pathology*. Philadelphia, 1925.
- Glycogen Accumulation.** GIERKE: *Ziegler's Beiträge*, 1929, **82**, 497; *Med. Klin.*, 1931, **27**, 576, 611. POMPE: *Ann. d'anat. path.*, 1933, **10**, 23. MOWRY AND BANGLE: *Am. J. Path.*, 1951, **27**, 611.
- Glycogen Disease.** VAN GREFFELD: *Archives of Disease in Childhood*, 1952, **27**, 113; *Medicine*, 1939, **18**, 1.
- Gout.** GUZZENT: *Klin. Wehnschr.*, 1926, **5**, 1069. MAGNUS: *Harvey Lectures*, 1909-1910, p. 251. STETTEN: *Bull. New York Acad. Med.*, 1952, **28**, 664.
- Hemochromatosis.** GILLMAN AND GILLMAN: *Arch. Path.*, 1945, **40**, 239. MALLORY: *Am. J. Path.*, 1925, **1**, 117; *Trans. Assn. Am. Physicians*, 1935, **50**, 12. MALLORY AND PARKER: *Am. J. Path.*, 1931, **7**, 351. SHELDON: *Lancet*, 1934, **2**, 1031; *Hemochromatosis*. London, 1935.
- Invisible Iron.** POPOFF AND POPOFF: *Yale J. Biol. and Med.*, 1943, **16**, 197.
- Lipotropic Factors.** BEST: *Science*, 1941, **94**, 523. MCHENRY AND PATTERSON: *Physiol. Rev.*, 1944, **24**, 128.
- Melanin.** DAWSON: *Edinburgh Med. J.*, 1925, **32**, 509. JACOBSEN: *Arch. Path.*, 1934, **17**, 141, 391. LAIDLAW: *Am. J. Path.*, 1932, **8**, 477. SPENCER: *Brit. Med. J.*, 1923, **2**, 907. STEWART AND HICKMAN: *J. Path. and Bact.*, 1931, **34**, 61. LERNER AND FITZPATRICK: *Physiol. Rev.*, 1950, **30**, 91. FITZPATRICK: *Arch. Dermat. and Syph.*, 1952, **65**, 379.
- Ochronosis.** POPE: *Lancet*, 1906, **1**, 24.
- Tissue Reaction to Lipids.** HIRSCH: *Arch. Path.*, 1941, **31**, 516.

## Chapter

### 3

## CIRCULATORY DISTURBANCES

THE circulation of the blood through a part may be interfered with in a number of ways, each of which adversely affects the particular tissue supplied: (1) there may be too much blood in a part or too little; (2) the vessel wall may be broken and the blood escape; (3) the blood may clot in the vessel and the clot may be detached and carried by the circulation so as to lodge in another vessel; (4) the fluid part of the blood may escape through the intact vessel wall and collect in the tissues. We have therefore to study: (1) hyperemia and ischemia, (2) hemorrhage, (3) thrombosis and embolism, and (4) edema. Hyperemia and congestion have the same meaning, but in practice the term hyperemia is usually applied to the active dilatation of arterioles and capillaries, as a result of which too much blood goes into the part, while congestion is applied to the passive dilatation of veins caused by some obstruction to the circulation, as a result of which too little blood gets out of the part.

### ARTERIAL AND CAPILLARY HYPEREMIA

Active hyperemia is a dilatation of the arterioles and capillaries, which may be dilated together or singly. It may be regarded as a physiological response to a call of the tissue for more blood. It must be realized that the capillary bed of an organ at rest is never all in operation at one time. In a healthy kidney only a limited number of glomeruli are working at any given moment, and it is only through the capillaries of these glomeruli that an active circulation is going on. The remainder remain collapsed. (Fig. 18). Whenever there is a call for more work the latent capillary bed becomes opened up. The same difference is observed between a muscle which has been actively contracting and one which is at rest. The active organ shows an active hyperemia. It has always been difficult to understand why in an organ of uniform structure, such as the liver, a blood-borne toxin tends to produce focal rather than diffuse lesions. The explanation appears to depend on the fact that some parts of the organ are relatively ischemic and therefore protected for a time from the injurious agent, while others are flooded with blood and thus exposed to damage.

Great active hyperemia of arterioles and capillaries is seen in inflammation. A comparison between the capillary bed in a normal and an inflamed omentum will soon prove the truth of this statement. In the early stages of pneumonia the vessels in the walls of the alveoli show an extreme degree of hyperemia. Inflammatory hyperemia is due to the direct action of toxins on the walls of the vessels, because it occurs when all the nerves to the part

are cut, and yet nervous influence does exert some influence upon it. Active hyperemia may largely disappear after death.

## VENOUS CONGESTION

Venous congestion or passive hyperemia is a condition in which the blood accumulates on the venous side of the vascular tree. The congestion may be general or local. Both of these may be acute or chronic. Of these various forms chronic general venous congestion is by far the most important.

### General Venous Congestion.—

**CAUSES.**—As the condition is general the cause must be central. There are only two organs through which all the blood in the body must pass. These are the heart and the lungs. Obstruction to the circulation through either of these organs will give rise to general venous congestion. As the obstruction is usually chronic in type the congestion will be chronic. In the *heart* the common cause is mitral stenosis, but mitral incompetence and aortic valvular disease will lead in the end to the same result. Chronic myocardial failure from whatever cause is also associated with chronic venous congestion.

In the *lungs* the chief causes of obstruction are emphysema and fibrosis. In emphysema there is great distention of the alveoli with destruction of the alveolar walls and narrowing of the capillaries in those which remain. The result is a marked obstruction to the pulmonary circulation with distention of the right side of the heart and accumulation of blood in the veins. Fibrosis of the lungs as the result of tuberculosis or other chronic infections also leads to obliteration of the pulmonary capillaries with resulting venous congestion.

These forms of congestion are of the chronic type. If cardiac failure is more acute, usually left ventricular in type, the venous congestion will also be acute. This type of failure often develops as a terminal phenomenon, and as the lungs are the first to suffer, it is seldom that autopsy fails to reveal some degree of pulmonary congestion.



FIG. 18.—The upper glomerulus is full of blood and active; the lower one is ischemic and resting.  $\times 200$ .

**EFFECTS OF CHRONIC VENOUS CONGESTION.**—These are both general and local. The *general effects* are due to insufficient oxygenation. Owing to accumulation of blood in the dilated veins the speed of the circulation is slowed down and the blood is not sufficiently aerated in the lungs. Moreover the edema of the lungs which so commonly develops still further prevents a proper interchange of gases. Owing to the resulting anoxemia there will be a varying degree of *dyspnea* or shortness of breath. As the blood remains unduly long in the venules and capillaries, there is a marked increase in the amount of reduced hemoglobin, the blood becomes more venous in type, and the patient manifests *cyanosis*, a blueness or lividity of



FIG. 19.—Nutmeg liver. The cut surface has a mottled appearance.

the skin and mucous membranes, well seen in the ears and lips. Cyanosis is seen in other conditions in which the blood is imperfectly oxygenated, especially in pulmonary disease and in congenital heart disease where an abnormal communication exists between the right and left sides of the heart. Owing to the general congestion the walls of the veins are injured and fluid escapes from the vessels into the tissues causing *edema*, especially in dependent parts such as the feet. Fluid may also pass into the serous cavities with the production of ascites, pleural effusion, etc.

The *local effects* are observed in the individual organs. These are described elsewhere, more

particularly in connection with the lungs, liver, spleen and kidneys.

**Local Venous Congestion.**—When the main vein from a region or an organ is obstructed a condition of local venous congestion is produced. The obstruction may be acute or chronic. *Acute obstruction* is usually due to thrombosis in the vein, but may also be caused by sudden pressure on the vein, as in strangulation of a loop of bowel, twisting of the pedicle of an ovarian cyst, etc. The result is very similar to the production of a hemorrhagic infarct which will be described presently. There is no time for a collateral circulation to be set up, so that there is intense engorgement of the venules and capillaries; many of these rupture, and there is hemorrhage into the part which becomes dark purple. Under the microscope the tissues are seen to be stuffed with blood. The condition is best observed in strangulation of the bowel, but may also occasionally be observed in the spleen, kidney, and other organs.

In *chronic obstruction* due to the pressure of tumors, enlarged glands, aneurism, etc., a collateral circulation is gradually established, so that the results are less severe. If the veins of the collateral circulation are superficial they can readily be seen and offer useful help in making a correct

diagnosis. Even when they cannot be seen with the unaided eye, they can be made visible by photographing the area using infra-red films. In obstruction of the superior vena cava these distended superficial veins are seen coursing over the clavicle and the upper part of the chest, while in the case of the inferior vena cava they pass upward on the abdominal wall. An important form of chronic local venous congestion is that due to obstruction of the portal vein, usually the result of cirrhosis of the liver. In *portal obstruction* the radicles of the portal vein become distended and varicose. Important varicosities are formed at the lower end of the esophagus and the lower end of the rectum. The latter form hemorrhoids or piles, and the former may rupture causing hemorrhage into the stomach which may prove fatal. Just as coughing of blood (hemoptysis) is a sign of pulmonary congestion, so vomiting of blood (hematemesis) is a sign of portal congestion. Fluid may pass from the branches of the portal vein into the peritoneal cavity causing ascites.

## ISCHEMIA

Ischemia is a local anemia, a cutting-off of the arterial blood supply to a part. It may be sudden or gradual. *Sudden obstruction* is, of course, produced when a vessel is ligatured, but in disease the usual causes are thrombosis and embolism. The result depends on the question of collateral circulation. If this can be established rapidly and adequately, blood reaches the part by other channels, and no serious damage is done. If such a circulation cannot be established, part or the whole of the area affected will quickly die. This change, which is well seen in the heart, spleen, kidney, and brain, is called infarction and will be studied in connection with the process of embolism.

*Gradual obstruction* is usually due to arteriosclerosis in which thickening of the intima leads to narrowing of the lumen. The area supplied atrophies, the parenchymatous tissue undergoes necrosis, disappears, and is replaced by fibrous tissue. This change is well seen in the kidney and the myocardium (ischemic necrosis). In the brain it leads to softening. Gradual obstruction of the arteries may also be produced by pressure from without, but this is of little importance apart from the pressure of splints and the formation of bed sores. Ischemia may be caused by prolonged arterial spasm in ergot poisoning and in Raynaud's disease, in both of which conditions gangrene of the extremities may develop.

**Anoxia.**—The cells of the body suffer from anoxia when they are unable to obtain sufficient oxygen or are unable to use it. Its effect is not only to stop the machinery but often to wreck the machine (Haldane). The following varieties may be distinguished: (1) *Stagnant anoxia* due to reduction in the flow of well-oxygenated blood. This is seen in ischemia, cardiac failure, and shock due to vasomotor collapse. (2) *Anoxic anoxia* due to insufficient oxygenation of the blood as it passes through the lungs, as seen in pneumonia and other widespread pulmonary lesions. (3) *Anemic anoxia* due either to reduction in the amount of hemoglobin or interference with its capacity to combine with oxygen, as in carbon monoxide poisoning.

(4) *Histotoxic anoxia* due to inability of the cells to utilize oxygen, owing to the action of such poisons as alcohol, narcotics and cyanide.

## HEMORRHAGE

Hemorrhage or the escape of blood from a vessel may occur from a variety of causes, some of which are simple, while others are obscure and indeed unknown. The hemorrhage may be due to a break in the wall of the vessel either from trauma or disease. In other cases there seems to be no distinct rupture of the wall, the red cells escaping out by a process of diapedesis. It is probable that many tiny hemorrhages occur in this way. The smallest hemorrhages, often no larger than a pin's head in size, are called *petechiæ*, while larger extravasations are called *ecchymoses*. When a hemorrhage of some size occurs into the tissue it may form a tumor-like swelling known as a *hematoma*.

Spontaneous massive hemorrhage is due to rupture of a vessel. The rupture may be caused by a local dilatation of the lumen with thinning of the wall (aneurism formation). A second class of case is the septicemias, in which petechial hemorrhages, particularly in the serous membranes, are of frequent occurrence. Here the probable cause is injury of the capillary endothelium by the bacterial toxins, although this is difficult to prove. In some instances (bacterial endocarditis, typhoid fever) clumps of bacteria may lodge in the capillaries and cause hemorrhage. A third group is that of the bleeding diseases which will be discussed in the chapter on the Blood. Some of the chief of these are pernicious anemia, leucemia, and purpura. In the last-named there is a great decrease in the number of blood platelets, but in none of them can it be said that we really know the cause of the hemorrhage.

**Changes in the Extravasated Blood.**—When the hemorrhage is very small, *i. e.*, petechial in type, the red cells may be removed by phagocytes. When it is of any considerable size the red cells are broken down so that hemoglobin is liberated, and this stains the surrounding tissues. The coloring matter of the hemoglobin is disintegrated into two moieties; one is iron-free and called *hematoidin*, the other contains iron and is therefore called *hemosiderin*. The hematoidin may be deposited in the form of granules or rhombic crystals which are seen around old cerebral hemorrhages, but some of it is converted into bilirubin which is soluble and therefore carried away and excreted in the bile. Large hemorrhages such as that of a ruptured tubal pregnancy may therefore be accompanied by jaundice. The hemosiderin is taken up by phagocytic cells, and these give the Prussian blue reaction for iron.

**The Arrest of Hemorrhage.**—This can best be studied in a vessel which has been divided. There is first temporary arrest of the hemorrhage by the formation of a blood clot, followed by permanent arrest due to the formation of an inflammatory exudate which becomes organized and seals the vessel.

The *temporary clot* is produced by the coagulation of the blood, a process which will be considered in connection with thrombosis. The temporary

clot is of two varieties, the red and the white. The *red clot* is composed of fibrin containing red cells in its meshes. The *white clot*, which is a thrombus, consists almost entirely of platelets, which form a sticky mass that adheres to the cut edges and serves to plug the hole in the vessel wall. The temporary clot is like a nail, the head of which is formed by the white clot and closes the cut end of the vessel, while the stem is formed by the red clot which extends along the vessel for some distance.

The *permanent clot* results from the organization of the temporary clot. As the result of the injury an inflammatory exudate is formed around the latter, new capillaries and fibroblasts grow in, the clot is vascularized and fibrosed, and the opening in the vessel is finally plugged by a mass of fibrous tissue firmly adherent to the edges of the hole. The arrangement just outlined is a singularly beautiful one, whereby the blood remains fluid in the vessels so that it can traverse the finest capillaries, yet the moment it is shed it clots and plugs the hole in the vessel wall. It is like a fire-sprinkler system, unnoticed as long as all goes well, but ready for any emergency at a moment's notice.

This process of healing only occurs properly in the absence of infection. If sepsis is present the formation of the permanent clot is interfered with, the temporary clot may be softened by the bacterial ferments, and *secondary hemorrhage* may occur one or two weeks after an operation. Before the days of asepsis such an accident was a common occurrence.

## THROMBOSIS

Thrombosis is the formation of a solid body, the thrombus, from the elements of the streaming blood. All the elements, platelets, fibrin, red cells, and leucocytes, may enter into the formation of a thrombus, but the first two are the most important. Thrombosis is quite different from clotting, although clotting may take part in the formation of a thrombus.

After death the blood clots in the heart, arteries, and veins but not in the capillaries. When blood clots in the larger vessels all the elements are involved, and the clot is soft and red, the "currant-jelly" clot. This type of clot is also seen in the heart when clotting is fairly rapid. But if it is slow the red cells fall to the bottom, and the clot consists only of leucocytes and fibrin. Such a clot is firmer and pale yellow in color, and is known as a "chicken-fat" clot. The lower part of the clot is often red and the upper part pale. Microscopically the clot has a characteristically homogeneous appearance. At first the individual red cells can be distinguished, but soon they become fused into a uniform structureless mass. The clot shows none of the delicate architecture of a thrombus.

**Mechanism of Thrombus Formation.**—Thrombosis is in essence platelet deposition, whereas clotting or coagulation is a reaction by which a sol, fibrinogen, is converted into a gel, fibrin, through the action of thrombokinase. As the platelets (thrombocytes) elaborate thrombokinase, it is evident that the two processes may be combined. If the blood flow is sufficient in volume and velocity to wash away the thrombokinase, clotting will not occur.



In a stained blood smear the platelets appear as small nuclear bodies arranged in clumps, but moving pictures of streaming blood show that the nucleus is a very small part of the platelet, and that it is surrounded for some distance by a thin veil-like cytoplasm which is actively amoeboid and throws out pseudopodia that are arrested by any irregularity of surface. Above a critical velocity the platelets are evenly distributed, but below it they show a remarkable tendency to stick together and to adhere to the intima, more especially if the intimal surface is roughened. When the number of platelets is increased (thrombocytosis) the stickiness is increased, because of the many young forms present. Heparin causes the platelets to lose their stickiness. Thrombocytosis always follows tissue injury,

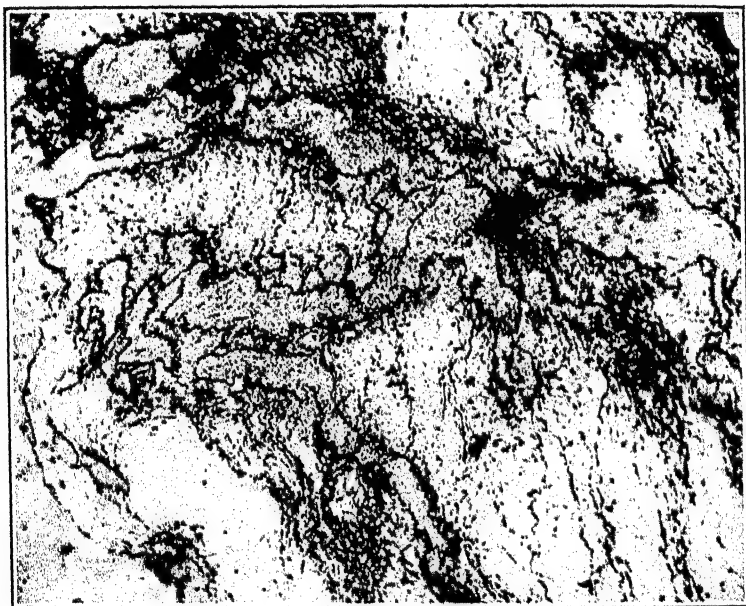


FIG. 20.—Antemortem thrombus, showing laminae of platelets outlined by fibrin and connected by fibrin threads. Fibrin stain.  $\times 100$ .

particularly that of parturition, fractures, and surgical operations. The greater the injury, the more marked is the thrombocytosis and the tendency to thrombosis.

As the platelets fall out of the streaming blood they form a kind of snow-drift, which smoothes over any roughness of the surface. Then a series of ridges or laminae of platelets grow across at right angles to the stream. These give to the thrombus the appearance of a piece of coral, and the edges of the laminae are seen as ripples known as the lines of Zahn (Fig. 22). Leucocytes stick to the laminae as flies to sticky fly-paper. The adherent platelets liberate thromboplastin, and this sets in motion the machinery of fibrin formation, so that festoons of fibrin threads hang between the ridges and entangle many red cells and more leucocytes (Fig. 20). The thrombus is now composed of platelets and fibrin with an admixture of red cells and leucocytes.

leucocytes (Fig. 21). In time the various elements are fused to form a hyaline mass.

When occlusion of the lumen occurs, true thrombosis ceases, because streaming blood is no longer available. Clotting, however, continues, and the clot is "propagated" to the next side branch if the vessel is an artery; the next tributary if it is a vein. This propagated soft red clot lies floating free in the lumen, though still anchored to the thrombus. In the case of a leg vein the propagated clot may be from  $1\frac{1}{2}$  to 2 feet in length. Propagation occurs when the stream is slow and sluggish. If it is rapid due to inflow from tributaries, a new platelet thrombus may be formed on the propagated fibrin clot, not the firm adherent platelet thrombus, that is likely to be detached and form an embolus.

**Causes.**—Thrombosis is the result of an upset in a delicate balance. Several things may cause this upset, some of which are known, some unknown. Of the known factors the two most important are slowing of the blood stream and injury to the intima.

(1) Thrombosis is much commoner in veins than in arteries. The venous circulation is a low-pressure, low-velocity system which is dependent on the strength of the left ventricle, the depth of respiration, muscular contraction, and the adequacy of the valves in the veins. Venous thrombosis may be a post-operative complication, but it is practically confined to patients with an ageing heart muscle. It is even commoner in congestive heart failure, especially when combined with general muscular immobility owing to the patient being confined to bed. Shallow breathing due to pulmonary disease, shock, or abdominal distension interferes with the venous flow and therefore predisposes to thrombosis. As Hadfield remarks, even in health there is only a narrow margin between movement and stasis in the outlying parts of the venous system, a margin which is dependent on general circulatory and respiratory efficiency. The vein walls are weak and thin, with little elastic tissue and therefore easily collapsed by pressure; they are superficial and easily injured; they are readily invaded by bacteria. In all these respects they differ from the deeply-placed arteries with their turbulent high-velocity flow, whilst in the intervals of flow the lumen remains empty, thanks to their thick elastic walls.

(2) Injury to the intima is the second important cause. This may occur in the arteries, the veins or the heart. In the arteries the smooth intima may be roughened by atheroma, which also narrows the lumen and slows the stream; it may become necrotic as the result of malignant hypertension, periarteritis nodosa, or disseminated lupus; or it may be injured by the surgeon's knife or ligature. In the arteries, with the exception of the aorta, there can, of course, be no propagated clot nor danger of embolism. The veins are liable to injury by trauma, by pressure, and by infection. In the heart the valves are injured by inflammation, so that thrombi are deposited on the surface.

Whilst injury to the intima and slowing of the blood stream are all important, there must be a third and unknown factor which determines why some people develop thrombosis and others do not. This may be a chemical change in the blood, possibly in the nature of a deficiency of heparin with resulting effect on the stickiness of the platelets.

**Sites.** Thrombi may form in the veins, arteries, heart, and capillaries.

**Veins.** The veins are the commonest site of thrombosis for reasons already given. The thrombosis may be divided into two groups: (1) venous thrombosis, and (2) thrombophlebitis. *Venous thrombosis* is by far the more important. It is associated with such factors as general circulatory failure, interference with respiration, and trauma. This is the type likely to be followed by pulmonary embolism, which may cost the patient his life. We have already seen that it is the soft friable propagated clot which is the source of danger rather than the firm adherent thrombus. About 40 per cent of instances of fatal pulmonary embolism occur in surgical cases, whereas 60 per cent occur in medical cases, but even in the surgical cases the causal factors responsible for the thrombosis are mainly medical in character. An exception is the increased number and stickiness of the platelets due to production of a large number of young forms. This occurs during the first week following operations or delivery; thrombosis and pulmonary embolism are most frequent between the fourth and tenth day. The common initial site of venous thrombosis is the deep veins of the calf muscles, with a propagated clot occupying the femoral vein. In fatal pulmonary embolism the veins of one leg may be filled with thrombus, whilst those of the other leg are empty. In such a case it is probable that the fatal embolus came from the empty vein. One barrel of the gun has been discharged; the other remains loaded. When a person is confined to a hospital bed the veins of the leg tend to collapse, and the pressure of the calf on a hard mattress brings the walls of the vein together with possible injury to the intima and liberation of thromboplastic substances which induce coagulation in the thin stream of blood that percolates through the crack-like lumen (Prykhodn). In support of this idea is the fact that during the bombing of London venous thrombosis of the leg veins with subsequent fatal pulmonary embolism occurred in elderly persons who spent long winter nights sitting in air-raid shelters on deck chairs which pressed on the back of the leg.

In 100 complete dissections of the veins of the pelvis and leg carried out by McLachlin and Paterson on middle-aged and elderly men, thrombi were found in 34 per cent of cases, in 56 per cent of which there was pulmonary embolism. Seventy-three per cent of the thrombi arose in the veins of the thigh and pelvis.

*Thrombophlebitis* has lost the importance it used to possess before the days of antiseptics and antibiotic therapy. Here the thrombosis is secondary to infection and inflammation of the vein wall (phlebitis). It is still seen in such conditions as cavernous sinus thrombosis in infection of the face and thrombosis of the pelvic veins in puerperal sepsis. The thrombus is firmly attached to the inflamed vein wall, so that there is no danger of massive fatal pulmonary embolism. Infection, however, causes the thrombus to break up, in which case there may be multiple small infected infarcts in the lung.

**Arteries.**—Arterial thrombosis is due to local causes, in distinction to venous thrombosis where such general causes as failing circulation and embarrassed respiration are important factors. Roughening of the intima due to atheroma is the common causal agent. The most frequent site is in

the coronary arteries, where the thrombus blocks the lumen, and may or may not lead to myocardial infarction, depending on the excellence of the collateral circulation. An atheromatous cerebral artery may become thrombosed, with softening of the brain. A thrombus may be deposited on an atheromatous patch in the aorta, and may be carried as an embolus into the arteries of the leg with disastrous results; this is the one example of embolism from an arterial thrombus. Inflammation or necrosis of the wall of an artery is likely to be followed by thrombosis; examples in the arteries of the leg are Buerger's disease, in the visceral arteries periarteritis nodosa, and in the arterioles malignant hypertension.

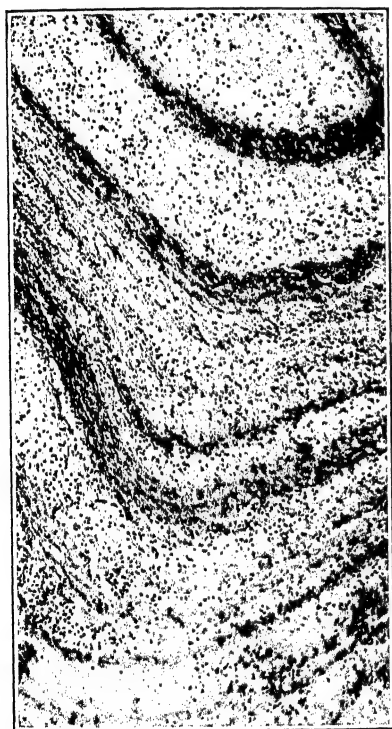


FIG. 21.—Antemortem thrombus. Numerous cells between the strands of platelets.  $\times 75$ .



FIG. 22.—Thrombus showing lines of Zahn.

*Heart.*—True thrombi are found in three sites in the heart. When the *valves* are inflamed (endocarditis), platelets are deposited on the roughened surface to form masses known as vegetations. On the necrotic surface of a *myocardial infarct* of the left ventricle a large thrombus may be deposited. In both of these cases portions of the thrombus may become detached and form emboli in the systemic circulation. In the *left auricle* a thrombus may form in mitral stenosis, owing to the eddying and poor flow of blood in the auricle due to the extreme narrowing of the lumen of the valve. (Fig. 23.) Postmortem clots are not true thrombi. They may be of the “chicken-

fat" type (firm and yellow) or the "currant-jelly" type (soft and red), depending on the rapidity with which they are formed.

*Capillaries.*—So-called capillary thrombi are hyaline masses formed by the fusion of red blood cells. There is, however, a very rare form of disseminated capillary and arteriolar platelet thrombosis due possibly to damage to the cement substance of the capillary wall, involving nearly every organ in the body, and progressing to a rapidly fatal termination. (Gore)

**CLINICAL EFFECTS.**—These depend on the organ and on the collateral circulation. When one of the main veins of the leg becomes thrombosed



FIG. 23.—Pale thrombi adherent to auricle and auricular appendix.

the vessel is tender and feels like a hard cord. Edema often develops, and the leg may be swollen from the foot to the thigh. Simple venous obstruction such as that produced by ligature of the femoral vein does not cause edema. Lymphatic obstruction is probably the deciding factor, and this is often present owing to spread of the infection from the vein to the lymphatics. Thrombosis of the portal vein is followed by a rapid accumulation of fluid in the abdominal cavity (ascites). Thrombosis of the superior mesenteric vein will produce the picture of hemorrhagic infarction with diffuse hemorrhage in the tissues. The same is true of the lung, and more rarely of the spleen and kidney. Thrombosis of the coronary arteries is followed by rapid necrosis of the area of myocardium involved, accompanied by severe cardiac pain and often followed by death. Thrombosis of the cerebral arteries causes softening of the brain. Finally the

thrombus or a portion of it may become detached from the vein in which it is formed and be carried into the general circulation where it constitutes an embolus.

**Subsequent Fate of the Thrombus.**—Much depends on the presence and degree of infection. If the thrombus becomes septic, *i. e.*, if it is infected with pyogenic bacteria, it will become softened and disintegrated, and may even be converted into an abscess. It is evident that in such a case the patient will be exposed to all the risks of pyemia. As a rule, however, the course is aseptic. *Contraction* of the thrombus occurs owing to the fibrin which it contains. The clot may shrink from the wall of the vein, leaving a space. *Absorption* of part of the thrombus may take place due to the activity of leucocytes. *Organization* is a common occurrence. This begins

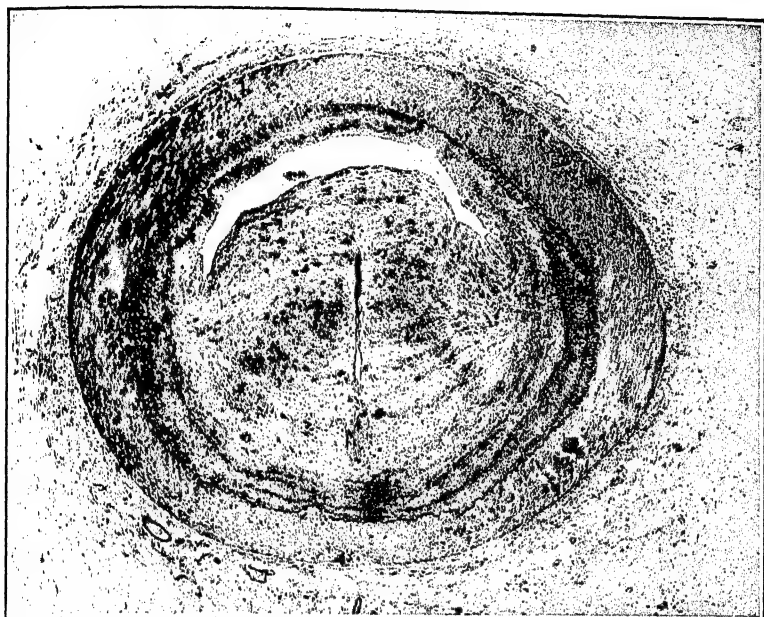


FIG. 24.—Thrombus in artery occluding most of the lumen, and becoming vascularized and organized.  $\times 30$ .

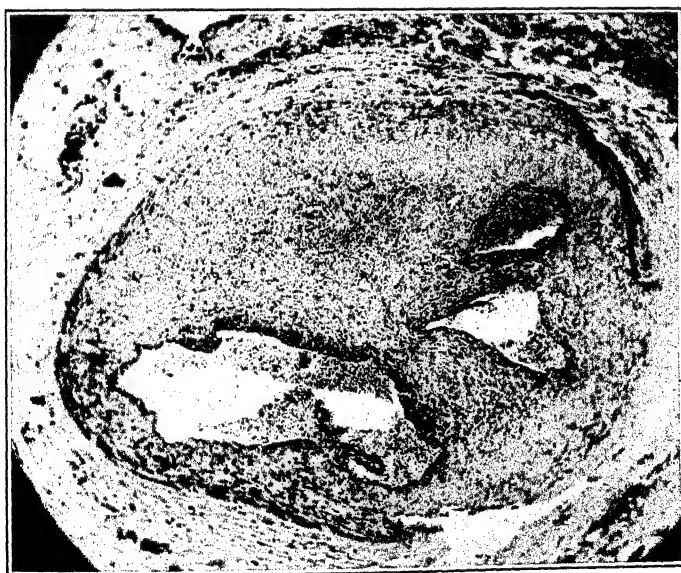


FIG. 25.—Canalization of an organized thrombus in an artery.  $\times 30$ .

at the point where the thrombus is attached to the vessel wall (Fig. 24). The process is the same as healing in a wound. New capillaries and fibroblasts grow in from the wall of the vessel, a vascular connective tissue is formed, and this is replaced by dense fibrous tissue. New channels may be formed through the fibrous mass and these become lined by endothelium (canalization). (Fig. 25.) If the clot shrinks from the wall of the vessel, the space formed is similarly refined. In this way the circulation may be in part reëstablished. Lime salts may be deposited in the thrombus to form a *phlebolith*. These calcified masses are often seen in the pelvic and prostatic veins in roentgen-ray pictures.

**Stasis.**—Kreyberg and other European workers have drawn attention to a condition which must be distinguished from thrombosis, although it is often confused with this process. When a part is chilled, as in frostbite, the smallest vessels are injured and when circulation is reëstablished they dilate and plasma pours out through their walls owing to increased permeability. As a result the erythrocytes in the minute vessels become conglutinated to form a homogeneous eosinophilic mass which blocks the lumen. Such a mass is commonly referred to as a hyaline thrombus, an unfortunate misuse of a term, for it is in no sense a true thrombus. To this process the name of stasis has been given. The process is of particular importance in frostbite, where it may lead to necrosis and gangrene owing to the anoxia produced.

## EMBOLISM

An embolus is a foreign body which is transported from one part of the circulatory system to another where it becomes impacted. The process is known as embolism. The usual form of embolus is a thrombus which has formed either in the heart or in the bloodvessels and has become detached from the wall (thromboembolism). Other forms of emboli are fat, air, tumor, bone marrow, amniotic fluid, atheromatous material and clumps of bacteria. These will be discussed separately. In addition to bloodvessel embolism, some consideration must be given to lymphatic embolism. Embolism is of interest for two reasons: (1) it is the means by which solid material is transported from one part of the body to the other, and is thus of great importance in the dissemination of tumors, bacterial infection, etc., (2) emboli may produce serious effects at their point of impaction.

*The source of the embolus* depends on the site of the thrombus from which it arises. In the heart there are three sites: (1) the auricle and auricular appendix, (2) a cardiac infarct in the left ventricle, (3) inflamed valves (the vegetations of endocarditis). The veins are of equal importance. Postoperative thrombosis is of special danger, and will be referred to presently in discussing pulmonary embolism. (Fig. 26.) The common sites of venous thrombosis have already been described in the previous section. In embolism following abdominal and pelvic operations the femoral veins must be carefully examined for thrombi. Thrombi in the right and left auricles, particularly in the auricular appendages, are not infrequently the source of emboli. An unusual form is the thrombus which

is developed on an atheromatous ulcer in the aorta, and is then carried further into the arterial tree.

**Infarction.**—When an embolus is impacted in an artery the effect is the same as if the vessel were suddenly closed by a clamp or ligature. This effect may be studied experimentally either by the use of artificial emboli such as seeds injected into the circulation or by clamping or tying the artery supplying the part. Everything depends on the *collateral circulation*, which in turn depends on the anastomosis between the affected vessel and the neighboring arterioles. In most parts of the body anastomoses are abundant so that when even a large artery is blocked an efficient collateral circulation is soon established; the palmar arch is an example of perfect collateral circulation. Ligature of the femoral artery is at first followed by blanching of the limb which becomes numb and cold. The anastomotic arteries undergo active dilatation, and blood finds its way into the ischemic tissue before any permanent damage is done. The collateral circulation must be maintained, *i. e.*, the dilatation is permanent. The walls of the dilated arteries become thickened to accommodate the increased pressure. It is evident that the efficiency of the collateral circulation will depend on two factors: (1) the state of the vessels, and (2) the strength of the heart. In an old person whose vessels are diseased owing to arteriosclerosis and whose heart is weak, the collateral circulation may be inadequate and gangrene will result. What has been said of ligature of an artery is equally true of obstruction from embolism.

An *infarct* is an area of coagulation necrosis resulting from a sudden arrest of circulation in the artery supplying an area without adequate collateral circulation. The word means a stuffing of blood (*infarcire*, to stuff), but this is not an essential feature of the process, depending on the collateral circulation and the looseness of texture of the part. It is only in the lung and the bowel that the part is stuffed with blood. In most of the viscera the anastomoses are less abundant than in the limbs.

After a transient initial period of hyperemia the infarct becomes ischemic and pale. The area is wedge-shaped owing to the fan-like distribution of



FIG. 26.—Thrombus at site of pelvic operation. Part became detached and caused fatal pulmonary embolism.  $\times 125$ .



the vessels. The collateral circulation endeavors to pour blood into the part, and owing to dilatation of the capillaries a hemorrhagic border is formed around the infarcted area. If this border is wide enough the entire area becomes hemorrhagic and stuffed with blood. An infarct may therefore be *pale* or *red*, the difference depending on the excellence of the collateral circulation. Infarcts of the kidney and heart tend to remain pale, those of the spleen tend to become red, while in the lung they are always red.

The redness is due to dilatation of the anastomotic vessels. Blood is forced into the collapsed vessels of the ischemic area, so that the part becomes stuffed with red cells. The overdistended vessels may give way, so that hemorrhage occurs. This is most marked in poorly supported capillaries such as those of the lungs and to a lesser degree in the spleen.



FIG. 27.—Infarct of kidney. The infarcted area is necrotic and is surrounded by a dark zone of congestion. Note the plugged artery.  $\times 8$ .

In about two hours the red cells become fused together into a homogeneous mass in which their outline can no longer be distinguished.

The tissues in the ischemic area undergo necrosis and die, and within forty-eight hours the infarct of the kidney is completely necrotic. (Fig. 27.) The necrosis is coagulative in type, so that dim outlines of the tubules and glomeruli may remain for a long time. The area is evidently kidney, but it is a city of the dead from which all life and activity have long since vanished. In sections the whole infarcted area stains diffusely with eosin, but at the margin nuclear remains may be seen, and the phenomenon of karyorrhexis is often very well marked. The nuclear fragments are apt to be mistaken for the nuclei of polymorphonuclear leucocytes. At the margin there is an extreme degree of hyperemia, and the hyperemic zone may be

of considerable width. The hyperemia may be attributed to the irritation produced by the dead tissue. In old-standing cases a zone of fibrous tissue may be formed around the infarct.

The gross appearance of an *infarct of kidney* is very characteristic. (Fig. 28.) An irregular area is observed on the surface, often slightly depressed and surrounded by a pink zone of hyperemia. The cut surface shows an area which may be wedge-shaped or irregular involving the whole width of the cortex and some of the medulla, pale in color and surrounded by a pink border.

In the *spleen* the process is very similar, but the collateral circulation is better, so that the infarct may be either red or pale. Old infarcts, however, are always pale, for the hemoglobin is gradually removed, the red cells disappear, and decolorization takes place.

*Infarction of the heart* is the result of thrombosis of one or more of the coronary arteries; only in very rare instances is it due to embolism. It constitutes one of the most important forms of heart disease, and is considered in detail in connection with diseases of that organ.

*Pulmonary embolism and infarction* are naturally very frequent, because an embolus which originates in the veins or in the right auricle will be arrested in the lungs. The condition is of great surgical importance because of the frequency with which it follows operations, especially operations on the female



FIG. 28.—Infarct of kidney. There are several pale areas of infarction in the cortex.

pelvis. In one large surgical clinic it is estimated that 7 per cent of the postoperative deaths over a series of years were due to this cause. It is necessary to distinguish between pulmonary embolism and infarction. There may be: (1) embolism without infarction, and (2) infarction without embolism. (1) A large embolus may occlude the pulmonary artery or one of its main branches (Fig. 29), and the patient dies of shock in a few minutes; in such a case there is no time for an infarct to develop. Death seems to be due to constriction of the pulmonary arterioles, as section of the sympathetic in animals prevents it. In a case of suspected pulmonary embolism special care must be taken with the autopsy. The pulmonary artery must be opened with the heart *in situ*, else the embolus is apt to be dislodged. The heart and lungs are then removed *en masse* and the branches of the artery carefully opened. A postmortem clot may be mistaken for an embolus. The embolus is more dry and brittle than the clot, and often shows a twisted, bent, or curled appearance which is very characteristic.

In an embalmed body the clot may be as dry as an embolus, but microscopic examination will show the more complex structure of a true thrombus (fused platelets, etc.). (2) On the other hand an infarcted area, an area stuffed with blood, may be produced by thrombosis of one of the pulmonary veins quite apart from embolism. Postoperative emboli may be divided into three groups: (1) Large emboli which occlude a main artery and cause death with acute respiratory distress in the course of a few minutes. (2) Medium-sized emboli which produce the physical signs of an infarct. (3) Small emboli which give rise to characteristic symptoms (sudden pain in the side, spitting of blood) but no physical signs. The accident usually occurs in the second week of convalescence, but may occur during the first two or three days. Pulmonary embolism may take place in the puerperium.



FIG. 29.—Pulmonary embolism. A twisted embolus occludes the pulmonary artery and its two main branches. The patient died in the course of a few minutes.

Belt has shown that pulmonary emboli are even more frequent than had been suspected. By careful dissection he had been able to demonstrate emboli in 10 per cent of autopsies. There is no other autopsy finding which is so easily missed. Embolism was found more often in medical than in surgical cases. In at least 60 per cent of the cases the emboli arose from thrombi in the veins of the leg and pelvis, most of which were unrecognized during life. The deep veins of the calf, which are usually not examined at autopsy, are perhaps the most frequent site of origin of the thrombus. The largest group was that of congestive heart failure—coronary, rheumatic or

hypertensive in origin. In most of the cases the venous thrombosis was spontaneous, and unassociated with any apparent inflammation in the veins. In a later communication Belt points out that recovery is not always complete after a nonfatal attack, for organizing emboli may produce cicatricial stenosis of the pulmonary arteries and thus lead to secondary thrombosis.

The use of anticoagulants such as heparin and Dicumarol, either singly or combined, has proved of great value in preventing fatal pulmonary embolism. The fatal embolus is often preceded by minor attacks of embolism, or the occurrence of venous thrombosis in the leg may be recognized clinically. Both of these are danger signals which may suggest the use of anticoagulants. Ligation of the veins in the leg has also been used

to prevent pulmonary embolism. A family history of thromboembolism is often of value in putting the physician on guard against this complication.

Infarcts of the lung are always red because the organ has a double blood supply. The bronchial artery supplies blood for nutrition at systemic pressure, whereas the pulmonary artery supplies blood for oxygenation at one-third of that pressure. The bronchial artery serves the important function of filling both circulatory beds with blood beyond an embolus. The collateral circulation is therefore abundant. Two results follow from this: (1) Occlusion of a pulmonary artery in a healthy lung is not followed by infarction, because of the abundant anastomosis. If the circulation



FIG. 30.—Infarcts of lung. Two infarcts are seen at the surface of the lower part of the lung. The artery passing to the lower infarct is filled by a pale embolus.

in the lung is impaired, as in chronic venous congestion, embolism readily results in infarction. In postoperative cases, particularly when the abdomen has been opened, there is always such impairment owing to interference with the respiratory movements and to the patient lying on his back. (2) The infarct is hemorrhagic and remains red. In course of time the infarct will disappear, but if the lung is inflated and careful search be made, small peripheral scars will often indicate the site of previous infarcts. Castleman has shown that these lesions can be detected in roentgen-ray films as fine white lines, whilst microscopically they can be recognized by the presence of irregular elastic fibers presenting a bizarre curley-cue arrangement. The infarct appears as a firm bright red, wedge-shaped area; the base of the wedge is at the surface and covered by a thin pleural

exudate. (Fig. 30.) The pleurisy is the cause of the characteristic pain in the side and the friction rub. The infarct is raised above the surrounding level and feels firm to the touch. The raised appearance is due to collapse of the surrounding lung when the chest is opened; if the chest is roentgen-rayed before being opened, the infarct will be seen to be depressed, not raised (Castleman). The cut surface is quite dry. The extent of the infarct varies enormously, often quite small, but sometimes involving the greater part of a lobe. Microscopically the alveoli are stuffed with blood, and their outlines are no longer visible, owing to necrosis of the alveolar walls. The presence of blood in the sputum is thus easy to understand.



FIG. 31.—Paradoxical embolism. The embolus is passing through a large foramen ovale into the left auricle.

Should the embolus be septic the element of infarction is obscured by the development of abscesses, usually multiple. The infected emboli may reach the right side of the heart *via* the superior vena cava (septic thrombosis of the lateral sinus and jugular vein, etc.), or *via* the inferior vena cava (septic thrombosis in the puerperal uterus, etc.).

*Embolism of the mesenteric artery* leads to infarction of the bowel and constitutes one of the acute abdominal catastrophes. The superior mesenteric is the vessel usually involved. The sudden loss of the blood supply of the bowel wall is followed by gangrene and other consequences which are described in Chapter 20.

*Cerebral embolism* leads to infarction of the brain and subsequent cerebral softening. Necrosis is followed by liquefaction, so that a cyst may be formed.

*Embolism of the central artery of the retina* results in sudden blindness with necrosis of the retina.

**PARADOXICAL EMBOLISM.**—This term is applied to the case where an embolus arises in a vein but lodges in a systemic artery instead of in the pulmonary artery. The occurrence is rare, but an important example of the so-called "crossed" embolism is cerebral embolism with hemiplegia following puerperal thrombosis of the pelvic and femoral veins. The usual explanation given is that the embolus has passed through a patent foramen ovale. If the foramen is really large this is possible, (Fig. 31), but in many of the cases the foramen is small or completely closed. In these cases the following possibilities may occur: (1) Clumps of bacteria may pass through the pulmonary capillaries and lodge in the cerebral vessels where they set up thrombosis with resulting softening of the brain and hemiplegia. (2) Infarction of the lung which is so common in puerperal thrombosis may cause thrombosis of the pulmonary vessels, and from this an embolus may arise which may pass to the brain. (3) An endocarditis on the left side of the heart may complicate puerperal sepsis, and the vegetations may form emboli which lodge in the brain.

**RETROGRADE EMBOLISM.**—Retrograde embolism is the plugging of a vein by an embolus moving in a direction contrary to the normal blood flow. Various explanations have been given of this rare occurrence, but none are satisfactory enough to warrant mention.

**FAT EMBOLISM.**—Globules of fat may enter the blood stream and lead to embolism. It is probable that fat gains entrance to the blood very frequently in fractures of bones, in operations on stout people, and in crushing injuries. During the Second World War Robb-Smith found pulmonary fat embolism to be a major lethal factor in 125 consecutive bombing casualties, and Wyatt and Khoo found fat emboli in every one of 30 persons who died as the result of trauma. The possibility must be borne in mind in all injuries to bone, and the fatal cases have been wrongly diagnosed as shock, coma, concussion, etc. There is no clinical correspondence between the apparent injury and the resulting lipemia which may be fatal. Direct trauma is not necessary, and fat embolism may occur as the result of osteomyelitis, suppuration of fatty tissues, burns of the skin and the convulsions of tetanus, eclampsia, and strychnine poisoning. The introduction of oil into the posterior urethra may cause fat embolism, especially if there has been previous urethral instrumentation, for the posterior urethra is an active absorptive bed. It may follow poisoning by phosphorus and potassium chlorate, and I have seen very extensive lesions in a young woman who had taken some poison either for suicidal purposes or to produce abortion. The fat enters torn veins, so that globules and cylinders of fat are found in the pulmonary capillaries, but unless frozen sections and fat stains are employed the fat will not be stained. (Fig. 32.) Small globules may pass through the pulmonary capillaries and lodge in the brain, the glomeruli of the kidney, etc. In the kidney the fat globules can be recognized as clear spaces in paraffin sections stained by ordinary methods. (Fig. 33) Fat regularly appears in the urine, a sign of diagnostic value. An even earlier sign is the presence of free fat and fat-granule alveolar cells in the sputum (Warthin). In the brain there are petechial hemorrhages in the white matter with a fat globule in the center of each. In the few cases in which symptoms appear, these usually come on at twenty-four hours and resemble those of surgical shock with pulmonary edema. There may be convulsions and coma from cerebral involvement, and death follows in some of the cases. Fat emboli of the coronary arteries may cause cardiac symptoms.

**AIR EMBOLISM.**—Air may enter the circulation as the result of artificial pneumothorax, or if one of the large veins in the neck is opened during an operation, etc. It occurs about once in every 500 to 1000 pneumothorax treatments. In the vast majority of cases no harm results. The rare fatal cases may be due to the air con-

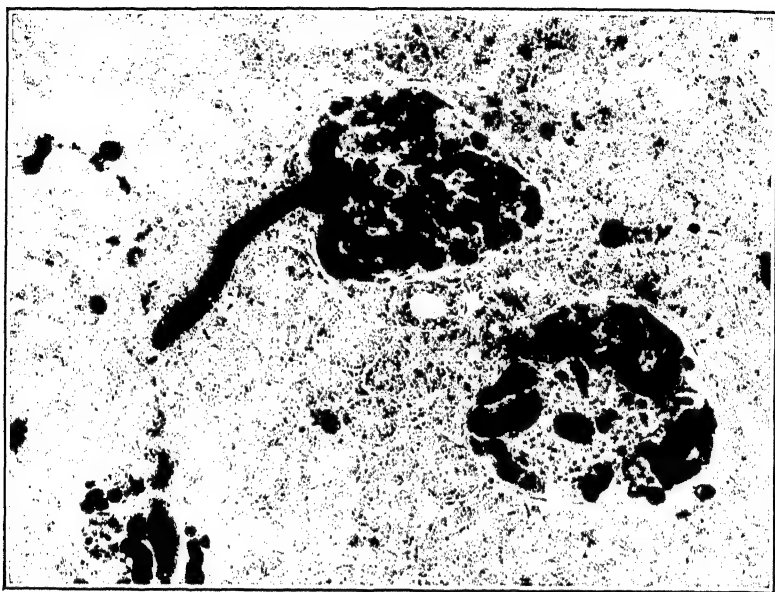


FIG. 32.—Fat emboli in kidney. Frozen section stained for fat.  $\times 100$ .



FIG. 33.—Fat emboli in kidney. Paraffin section. The spaces represent fat which has been dissolved out.  $\times 200$ .

latter it is general. When water collects in the tissues it may be in free or combined form. When combined it is united with the protoplasm of the tissue elements. When free it lies between these elements and can be moved from one place to another. For this reason a pit is left when an edematous part is pressed on; this is known clinically as "pitting on pressure." Sometimes there is a solid edema, in which case there is no pitting on pressure. The water is taken up mainly by the connective tissue of the muscles and skin, or rather the subcutaneous tissue. An initial accumulation of water cannot be detected clinically. Indeed it is only when 5 or 6 liters have collected in these water depots that edema becomes evident. But this invisible accumulation of fluid is indicated by a steady increase in weight.

The volume of water in the blood must be kept constant, so that it is not allowed to accumulate within the vessels. When a person drinks a large quantity of water it is absorbed in the blood, but rapidly passes out into the tissues and is retained in the water depots. It must be remembered that in a person of average weight there are 35 kg. of water in the body, but that only 5 of these are in the blood while 30 are in the tissues. As the kidneys excrete water from the blood, the water in the tissues passes back into the blood. The water in its passage must traverse the walls of the capillaries. Some of the fluid in the tissues is carried off by the lymphatics. It will thus be seen that the amount of fluid in the tissues depends on the following factors: (1) the amount of fluid ingested; (2) the condition of the capillary walls, with which may be included the condition of the circulation; (3) the condition of the tissues (distribution of electrolytes, concentration of sodium chloride, degree of oxygenation, amount of acidosis, etc.); and (4) the condition of the kidneys. There is in addition the question of a nervous regulatory mechanism of water exchange which may be disturbed. The complexity of the problem now becomes evident, and the impossibility of stating with certainty which factor or factors are at fault in any particular case.

Edematous fluid closely resembles lymph; the one is normal, the other abnormal, interstitial fluid. It contains less proteins, and the specific gravity is lower—1.006 to 1.012. It does not readily coagulate when removed from the body, but sometimes a thin clot may form. No clotting occurs within the body (*e. g.*, in the serous cavities). At the same time it must be recognized that the composition varies with the mode of production and the etiological agent. A distinction may be drawn between a transudate and an exudate. A *transudate* is ordinary edematous fluid; the specific gravity is below 1.015 and the protein below 3 per cent. An *exudate* is the fluid of an inflammatory edema; the specific gravity is above 1.018 and the protein above 4 per cent. Clotting is more marked when the fluid is removed from the body, and may occur within the serous cavities. It is evident that an exudate more closely resembles blood plasma than does a transudate.

*Tissue Changes.*—An edematous tissue has a pale watery appearance. Subcutaneous tissue may come to resemble jelly. In the lung where edema of the alveoli is very common, the affected part may feel solid, but fluid pours from the cut surface. The brain acquires a characteristically wet



appearance. Under the microscope the tissue elements are widely separated by watery material which can be best demonstrated if the tissue is fixed in boiling formalin so that the fluid does not escape. In well-fixed specimens the fluid appears as fine granules. The fluid of edema is not always intercellular. Cells and fibrin may become edematous and swollen; the change is similar to hydropic degeneration.

**Varieties of Edema.**—Fluid may collect in the tissues under a variety of conditions which bear no relation to one another. Edema may be local or general. Of course, in general edema the condition may be more pronounced in one locality, but the etiological agent acts generally. The main forms of edema are *inflammatory*, *obstructive*, *cardiac*, and *renal*. Inflammatory and obstructive edemas are local, cardiac and renal edemas are general. To these must be added *angioneurotic* and allied forms of edema; also the edema of *chronic starvation* and that variety of it known as *war edema*. Instead of taking these up *seriatim* it will be better to consider the various factors which may cause edema, and then return to the special forms of the condition.

**Causes of Edema.**—There are three main causes of general edema, and a fourth factor which comes into play in local edema. In addition to these there are a number of secondary factors which will have to be considered. The primary factors in general edema are: (1) Increased permeability of the capillary wall, (2) decrease of the colloid osmotic pressure of the plasma proteins, and (3) increase of the capillary blood-pressure. The additional factor in local edema is (4) lymphatic obstruction.

1. INCREASED PERMEABILITY OF THE CAPILLARY WALL.—The normal capillary wall is a semipermeable membrane through which water and salts can pass in either direction with the greatest ease. Much has been written about increased permeability of the vessel wall as a cause of edema, especially in inflammation. The endothelial wall cannot become more permeable to water and crystalloids, because it already is completely permeable. Moreover, the rate of passage of these materials and their amount is independent of the condition of the capillary wall, being determined entirely by forces on either side of the wall, either in the blood or in the tissues. But the outward passage of colloids is intimately related to the condition of the vessel wall. Under normal conditions protein is prevented almost completely from passing from the blood into the tissues, but when the vessels are injured by toxins, lack of oxygen, etc., they become readily permeable to protein, as is seen in inflammatory edema. In the kidney this causes albuminuria, while elsewhere there is what Eppinger has called "albuminuria into the tissues." The passage of the large protein molecules is favored by dilatation of the capillaries, due in turn to relaxation of the branching Rouget cells, and Krogh believes that this is one of the major factors responsible for the great escape of protein in the edema of inflammation.

The escape of protein is of the greatest importance in the production of edema, for it lowers the colloid osmotic pressure of the blood and raises that of the tissues, as a result of which water readily passes out through the capillary wall. The increased permeability to protein is thus a major factor in the production of edema.

2. DECREASE OF THE COLLOID OSMOTIC PRESSURE OF THE PLASMA PROTEINS.—We have seen that the water of the blood can escape with the greatest ease into the tissues. The force which holds it back is the colloid osmotic pressure of the proteins. If an animal is bled repeatedly but kept alive by reinjection of the red blood cells, the plasma proteins will fall to a low level and marked edema will develop. A fall of plasma protein below 5 per cent will cause edema. For this reason long-continued anemia is apt to be associated with edema. Marked ascites, when the fluid is rich in protein, as in malignant disease of the peritoneum, may lead to generalized edema (anasarca) owing to the severe plasma-protein loss. The different proteins of the plasma have different colloid osmotic pressures, albumin being about four times stronger than globulin. It follows that when there is a great loss of albumin from the blood, as in the albuminuria of chronic Bright's disease (wet nephritis, nephrosis), with a reversal of the normal albumin-globulin ratio (3 to 1), edema will result. The colloid osmotic pressure depends therefore partly on the total amount of plasma proteins, partly on their relative proportion.

3. INCREASE OF THE CAPILLARY BLOOD-PRESSURE.—The pressure in the capillaries is the force which overcomes the colloid osmotic pressure of the plasma and enables the normal passage of nutritive fluid into the tissues. If it is increased, edema will result. The pressure in the capillaries depends upon the venous blood-pressure and not upon the arterial pressure. In cardiac failure the venous pressure rises markedly, and the increased capillary pressure leads to edema. The stretching and dilatation of the capillaries also renders them more permeable. The edema which follows thrombosis of the main vein of a limb is largely due to an increase in the capillary blood-pressure. It must not be thought, however, that fluid can only leave the blood through the capillaries. Rous and his associates have shown that in the case of the skin the permeability of the vessels to a slowly diffusible vital dye is much greater in the venules than in the capillaries. There is a mounting grade of permeability along the capillaries, being lowest at the arterial and highest at the venous end.

4. LYMPHATIC OBSTRUCTION.—This is an important factor in the production of local but not general edema. Much of the intercellular fluid in the tissues escapes by way of the lymphatics, so that obstruction to outflow through these channels will cause local edema. The obstruction may be due to inflammation, the presence of tumor cells within the lumen, or *Filaria bancrofti*, a parasitic worm which may block the channel. Pressure from without produces the same effect. This pressure may be due to a tumor or to collection of fluid. As the fluid increases the lymphatic obstruction becomes more marked, so that a vicious circle is formed. For this reason removal of part of an effusion in a serous sac is often followed by disappearance of the remainder, for reduction of the pressure allows the lymph channels to be opened up and the fluid to be drained away. Examples of lymphatic edema are the swelling of the arm which may develop in cancer of the breast; *elephantiasis* or swelling of the legs, scrotum, etc., seen in most marked form in obstruction due to filaria; *chylous ascites* and *chylothorax*, effusions of chylous fluid in the abdominal and pleural cavities due to obstruction of the thoracic duct by filaria, tumors, enlarged glands,

etc. *Non-parasitic elephantiasis* is an edema of the leg occurring mostly in young women, due apparently to chronic lymphangitis of unknown origin. *Milroy's disease*, or hereditary edema, is also probably lymphatic in origin.

*Secondary factors* are the osmotic pressure in the tissues and chloride retention due to renal insufficiency. It is evident that if the protein of the plasma escapes through the capillary wall the *colloid osmotic pressure of the tissue* will rise, and on that account water will pass out of the vessels. *Chloride retention* is a secondary but not a primary factor; it aggravates and continues an already existing edema, but does not initiate the condition. But although salt retention is not a primary factor in the production of edema, yet once the condition of edema is established and the chlorides pass into the tissues with the water, the greater the amount of salt available, the more water will be retained in the tissues because of the increase of the osmotic pressure there. That there is a real relation between salt retention and edema is shown by the fact that in renal edema the withdrawal of salt from the food is often followed by rapid disappearance of the edema and a corresponding increase in the flow of urine.

With these additional facts in mind we may briefly review some of the various forms of edema which have already been mentioned.

**Inflammatory Edema.**—The swelling which is one of the cardinal signs of inflammation is largely due to edema. Owing to the action of the irritant the permeability of the capillaries is increased and fluid pours out into the intercellular spaces. This fluid is rich in protein. Owing perhaps to the formation of a network of fibrin the fluid cannot be moved about through the tissues as in other forms of edema, nor is it influenced by gravity. There are other factors besides injury to the vessel walls, but these and other matters connected with the edema of inflammation are discussed in detail in the next chapter. If the inflammation involves the pleura, pericardium, or peritoneum these serous sacs are filled with fluid from which fibrin is deposited on the surface.

**Cardiac Edema.**—This might better be called congestive edema, for it is apt to develop in any long-standing condition of venous congestion, though usually due to progressive cardiac failure. The obstructive edema seen when a large vein becomes thrombosed belongs to the same group. The fluid is loose in the tissues and readily changes its position under the action of gravity, so that it first appears in the dependent parts. The serous sacs become filled with fluid. For some reason the effusion is much commoner in the right pleural sac than in the left. Several factors are probably at work. Owing to the failing circulation there is an increase of pressure in the veins and capillaries. For the same reason there is back pressure in the lymphatics. The capillary walls are stretched and rendered more permeable. Oxygenation is poor and the vascular endothelium suffers in consequence and fails to hold back the water, but this factor is probably not of much importance, else the proteins would come through in larger amounts.

*Pulmonary edema* is a variety of cardiac edema. As the left side of the heart fails, blood accumulates in the lungs and fluid passes from the distended capillaries into the alveoli. The condition is most marked in the

dependent parts of the lung. The changes are described in the section on the Lungs.

**Renal Edema.**—This resembles cardiac edema except that the fluid is less influenced by gravity. Nor are the serous sacs involved so soon. The protein content and specific gravity are much lower than in cardiac edema, indeed lower than in any of the edemas. Blood examination will at once differentiate the two, for in edema due to chronic nephritis the blood cholesterol is markedly raised, while in cardiac edema it is normal. Renal edema is seen in acute nephritis, in the subacute or wet stage, and in the condition known as nephrosis, which is probably merely a variant of true nephritis. In all of these the edema is associated with marked albuminuria but not with a high blood-pressure. Indeed as the blood-pressure goes up the edema tends to disappear. A number of factors appear to be responsible. In wet nephritis and nephrosis there is a fall in the blood proteins and a reversal of the normal (3 to 1) albumin-globulin ratio; both of these reduce the osmotic pressure in the blood so that water passes into the tissues. Crystalloids, especially sodium chloride, are retained in the tissues and raise the osmotic pressure there, so that when water is drunk it passes into the tissues instead of into the urine, what Fishberg calls a prerenal deviation of water.

**CACHECTIC EDEMA.**—In many wasting diseases and anemias edema develops in the later stages, affecting the feet and legs particularly. Several causal factors may be at work. There is likely to be cardiac exhaustion and circulatory failure, the nutrition of the vessel walls is interfered with, the blood proteins especially in anemia are lowered and the osmotic pressure falls.

**FAMINE EDEMA.**—In prolonged undernutrition and chronic starvation edema may develop. This was common among prisoners on the Continent during the First World War. The blood proteins are very low owing to absence of proteins from the diet, so that the osmotic pressure falls and fluid leaves the bloodvessels. It is probable that absence of vitamin A has something to do with it, because in many cases there develops the ulceration of the cornea (xerophthalmia) characteristic of deficiency of that vitamin.

**HEREDITARY EDEMA. MILROY'S DISEASE.**—This is a chronic edema without any evident cause or constitutional disturbance. It is markedly hereditary. Milroy observed 22 cases in a family of 97 individuals (six generations). It is confined to the lower limbs, affecting one or both legs. The leg may be very greatly swollen. The condition should be distinguished from the non-parasitic form of elephantiasis, a condition which is usually confined to women, whereas Milroy's disease is equally common in both sexes.

## SHOCK

The basis of shock is essentially a circulatory disturbance, so that it may be considered here. This mysterious and sinister condition is liable to develop after: (1) extensive operations, particularly those involving handling of the abdominal viscera; (2) acute abdominal catastrophes (perforation of stomach or bowel, strangulated hernia, acute pancreatitis); (3) severe injuries; (4) extensive hemorrhage. The condition has continually to be guarded against by the surgeon, and is of special importance in war injuries.

The appearance of a person in shock is characteristic. He lies quite still, apparently unconscious of his surroundings, but can answer questions slowly and correctly. The face is pale and gray, drawn and anxious, and the skin is cold and clammy. The temperature is sub-normal, the pulse feeble, the respirations shallow and sighing, and the blood-pressure alarmingly low. Shock fortunately may be only a temporary condition; it is a step toward death, but a step which the patient can retrace in a few hours.

CAUSES.—Moon puts the matter in a nutshell when he remarks that the shock syndrome results from a disparity between the volume of blood and the volume-capacity of the vascular system. There may be a decrease in the blood volume, an increase in the volume-capacity of the vascular system, or a combination of these. The blood volume may be decreased by hemorrhage, and by transudation of serum through the capillary walls with resulting increased concentration and viscosity of the blood and rise in the red cell count and hemoglobin percentage (an important factor in shock due to severe burns). Shock is a circulatory deficiency characterized by decreased blood volume, decreased cardiac output, and increased concentration of the blood.

A distinction must be drawn between *primary shock* which follows immediately on the receipt of a severe injury and *secondary shock* which may not develop for twenty-four hours. In primary shock the chief factor is the discharge of nociceptive nervous stimuli which lead to *widespread capillary paralysis*. In secondary shock the commonly accepted explanation of the capillary paralysis is the widespread action of a histamine-like substance liberated as a result of the bruising of muscles. During World War I Bayliss and Cannon showed that experimental bruising of muscles in animals was followed by shock, but if the main vessels of the limb were first tied no shock developed. Injection of extract of the bruised muscles produced the same effect. Dale has shown that the *injection of histamine*, a cleavage product of protein, produces an identical result. The observations of Blalock have thrown doubt on this explanation of secondary shock. Blalock points out that bruising of muscles is accompanied both by hemorrhage into the part and by a great extravasation of serum due to increased permeability of the capillaries. There is therefore a great decrease in the volume of the blood with resulting shock. *Accessory factors* undoubtedly play a part. Thus cold, exhaustion, depression, and general anesthesia (especially ether and chloroform) predispose to the development of shock.

**Nature of Shock.**—Shock, like eclampsia, might be called “the disease of theories,” and several pages might be filled in discussing them. It is probably a mistake to look for a single causal factor; in most cases of shock in man a variety of factors come into play. The essence of the condition seems to be a relative disappearance of blood from the heart and great vessels, so that the heart has not sufficient fluid on which to contract. Much used to be written about “the mystery of the lost blood.” In shock due to hemorrhage there is of course no mystery. In other cases it is now known that the blood has disappeared into the vastly dilated capillary bed or into the tissues owing to transudation of serum. The patient may therefore be said to bleed into his own capillaries or into his tissues.

In a state of health only a small amount of the capillary bed is open at any one time. The blood flows through only a limited number of glomeruli in the kidney at the same time. According to Krogh the volume of blood in the active muscles of a guinea-pig may be 275 times as great as when the muscles are at rest, and if the entire capillary bed were opened up there would be 750 times as much blood. If, then, something can paralyze the vast capillary bed of the body and cause it to dilate, the blood will disappear into it as if sucked up by a sponge, the blood-pressure will fall, the heart will be unable to beat properly, and the brain will suffer from anemia.

The *lesions* are those which might be expected from these general considerations, as Moon has shown both in the experimental animal and in man. They are most marked in the lungs and the gastrointestinal tract. The lungs are dark and filled with blood. The liver and gastro-intestinal tract are intensely congested. All this is in marked contrast to surface structures, which are pale and bloodless. Microscopically the pulmonary capillaries are widely dilated and the alveoli are filled with fluid; it is a picture of pulmonary congestion and edema. In the wall of the intestine the increased capillary permeability is evidenced by petechial hemorrhages and edema. Similar lesions are found in fulminating influenza and severe burns, conditions in which the clinical picture is one of shock. The lesions are thus the reverse of those seen in severe hemorrhage.

### ADDITIONAL READING

- Air Embolism.** HAMILTON AND ROTHSTEIN: J. A. M. A., 1935, **104**, 2226.
- Bone Marrow Embolism.** FISHER: Arch. Path., 1951, **52**, 315. RAPPAPOORT *et al.*: Am. J. Path., 1951, **27**, 407.
- Capillaries.** KROGH: Anatomy and Physiology of Capillaries. New Haven, 1922. LANDIS: Heart, 1930, **15**, 209. LEWIS: The Blood Vessels of the Human Skin and Their Responses. London, 1927. MUFSON: Am. J. Med. Sci., 1932, **183**, 632. SMITH AND ROUS: J. Exper. Med., 1931, **54**, 499. WRIGHT AND DURYEE: Arch. Int. Med., 1933, **52**, 545.
- Clotting of Blood.** DE TAKATS: Arch Surg., 1944, **48**, 105.
- Congenital Hydrops.** FERGUSON: Am. J. Path., 1931, **7**, 277. WANSTROM: Am. J. Path., 1933, **9**, 623.
- Edema.** ELWYN: Am. J. Med. Sci., 1930, **180**, 781.
- Fat Embolism.** BIENCKE: Beitr. z. path. Anat. u. z. allg. Path., 1897, **22**, 343. GAUSS: Arch. Surg., 1924, **9**, 593. VANCE: Arch. Surg., 1931, **23**, 426. WARREN: Am. J. Path., 1946, **22**, 69. WARTHIN: Internat. Clin., 1913, **4**, 171.
- Heparin.** BEST: Brit. Med. J., 1938, **2**, 977. HOWELL: Physiol. Rev., 1935, **15**, 435. JORPES: Heparin: its Chemistry, Physiology and Application in Medicine. London, 1939.
- Histamine.** DALE, LAIDLAW AND RICHARDS: Medical Research Council, Special Report Series, No. 26, 1919; J. Physiol., 1918, **52**, 112; 1918-1919, **52**, 355.
- Infarction.** KARSNER, *et al.*: J. A. M. A., 1911, **57**, 951; J. Med. Res., 1912, **27**, 205; 1916, **34**, 21; J. Exper. Med., 1913, **18**, 507.
- Paradoxical Embolism.** BARNARD: Quart. J. Med., 1929, **23**, 305. THOMPSON AND EVANS: Quart. J. Med., 1929, **23**, 135.
- Pulmonary Embolism.** BELT: Am. J. Path., 1934, **10**, 129; Brit. Heart J., 1939, **1**, 283; Lancet, 1939, **2**, 730. HOLMAN, *et al.*: Arch Surg., 1929, **19**, 1246; J. Thor. Surg., 1932, **1**, 339. WHARTON AND PIERSON: J. A. M. A., 1922, **79**, 1904.
- Pulmonary Infarct.** CASTLEMAN AND HAMPTON: J. Tech. Methods, 1941, **21**, 5.

- Shock.** BLALOCK: Arch. Surg., 1930, **20**, 959. CANNON: Traumatic Shock. New York, 1923. MOON: Ann. Int. Med., 1935, **8**, 1633; Arch Path., 1937, **24**, 642; Am. J. Med. Sci., 1942, **203**, 1, Shock and Related Capillary Phenomena. New York, 1938. MOON: Shock. Its Dynamics, Occurrence and Management. Philadelphia, 1942. O'SHAUGHNESSY AND SLOME: Brit. J. Surg., 1934-1935, **22**, 589. RUKSTINAT: Arch. Path., 1932, **14**, 378.
- Stasis.** ROTNES AND KREYBERG: Acta path. et microbiol. Scandinav., Supp. 1932, **11**, 162.
- Thrombosis.** FRYKHOLM: Surg., Gynec. and Obst., 1940, **71**, 307. SILBERBERG: Physiol. Rev., 1938, **18**, 197. WRIGHT: J. Path. and Bact., 1942, **54**, 461.
- Thrombosis and Embolism.** COHNHEIM: Lectures on General Pathology (English translation). London, 1889. WELCH: Allbutt and Rolleston's System of Medicine, 1909, **6**, 691, 762. McLACHLIN AND PATERSON: Surg., Gynec. and Obst., 1951, **93**, 1.

## Chapter

### 4

## INFLAMMATION

INFLAMMATION is the most common, the most carefully studied, and the most fascinating of the changes which the body undergoes as the result of disease. Its history is the history of pathology. For two thousand years it remained an enigma. Not until Virchow laid the solid foundation of modern pathology by his doctrine of Cellular Pathology was it possible to solve the riddle of the sphinx. And yet at the present day there is no subject in the whole of pathology which is more thoroughly understood, although there are still many fundamental problems which demand investigation. "For the development of the sound pathologist," as Adams remarks, "a full knowledge of the factors concerned in the inflammatory process and a right appreciation of the doctrine of inflammation is as essential as to the orthodox theologian is a right attitude in respect to the doctrine of the Trinity."

DEFINITION.—Inflammation is the local reaction of the body to irritation. There is a general reaction which will be considered later under the heading of Infection. The local inflammatory reaction presents two phases. The object of the first is to destroy and remove the irritant; the object of the second is to repair the damage done to the tissues. The first is subserved by the wandering mesodermal cells whether of the blood or the tissues, the second by the fixed cells of the part. (The use of the teleological term "object" may be forgiven on grounds of convenience. In a physico-chemical process such as inflammation there is no good or bad, but merely cause and effect.) Many pathologists confine the term inflammation to the first of these processes, considering the second as a manifestation of repair. Such a procedure is quite justifiable, but we prefer to adopt the wider concept. Degeneration of varying degree is always present. The histological picture of inflammation is therefore made up of three features, although differing greatly in intensity; these features are degeneration, exudation and proliferation.

CAUSES.—From our definition it is evident that any irritant may act as a cause of inflammation, so that a full list of causes would include every known irritant. These irritants may be divided into two great groups, the living and the non-living. Of the *living* irritants by far the most important are the pathogenic or disease-producing microorganisms. Of less importance are the animal parasites. Both of these act as irritants mainly by virtue of chemical poisons which they produce, and to a lesser degree by the mechanical irritation which they excite. The pathogenic bacteria usually excite an acute reaction, as a result of which both the cells and the fluid



part of the blood pass from the vessels into the tissues. Some produce a more chronic form of reaction, characterized in the main by proliferation of the tissue cells; examples of such chronic irritants are the microorganisms of tuberculosis and syphilis. These chronic inflammations constitute the important group of the granulomata. The *non-living* irritants may be divided into physical and chemical. Among the *physical* irritants may be mentioned trauma, the presence of a foreign body, the action of undue heat and cold (burns and frostbite), of pressure, of light, of electricity, of roentgen-rays, of the radiations from radium, etc. *Chemical* irritants include strong acids and alkalis, and poisons of every description.

In the discussion which follows it should be borne in mind that there is no hard and fast line between an irritant and a stimulant. If an irritant is sufficiently weakened it becomes a stimulant. It follows, therefore, that while at the center of the inflammatory stage we shall find every evidence of intense irritation, away at the wings the tissues may respond as to a stimulant.

**The Essence of Inflammation.**—The word inflammation takes us back a long way in the history of medicine. Literally it means a burning. The condition was studied clinically hundreds of years before any true insight was obtained as to the inner pathological meaning of the process. It was Celsus in the first century A.D. who named the famous “cardinal signs” of inflammation as calor, rubor, tumor and dolor in words which have subsequently become celebrated: “Now the characteristics of inflammation are four—redness and swelling, with heat and pain.” In the course of time it became evident that these cardinal signs were the outward expression of vascular changes. In the middle of the nineteenth century Cohnheim applied the experimental method to the study of inflammation and showed with a brilliance and conclusiveness which left no room for doubt the all-important part played by the vessels in the process.

But the vascular changes are not the essence of inflammation. It remained for Metchnikoff in 1892 to demonstrate in his great work on the Comparative Pathology of Inflammation that the central theme of inflammation was the reaction of the wandering mesodermal cells against the irritant. In the higher animals which possess a vascular system these cells are for the most part contained within the bloodvessels. They are the leucocytes of the blood. The object and meaning of the vascular phenomena is to bring these mesodermal defense cells from the interior of the vessels to the outside where they can meet and cope with the irritant. The vascular changes are very striking; for the clinician they provide the cardinal signs of inflammation, but they are not essential. In a non-vascular tissue such as the cornea the wandering cells of the part gather around the irritant and cope with it just as surely as if they had come from inside the vessels.

In man and other vertebrates the mesodermal cells of defense may be divided into the wandering cells of the blood (the leucocytes) and the resting wandering cells of the tissue. It is the former which play the major part in the earliest stages of acute inflammation. Moreover there is a humoral factor of defense as well as a cellular factor, and the constituents of the humoral factor are contained in the blood plasma. It thus becomes neces-

sary for both the white blood cells and the blood plasma to escape from the interior of the vessels in order that they may reach the irritant. This escape is brought about by the vascular phenomena of inflammation.

**The Vascular Phenomena.**—We owe our present complete knowledge of the vascular changes in inflammation to the experimental researches of Cohnheim, whose *Lectures on General Pathology*, published in 1877 and now available in English translation, should be consulted by anyone interested in inflammation. It is remarkable how little has been added by subsequent observers.

Cohnheim's method was to draw out the intestine of a curarized frog through an opening in the abdominal wall and spread the mesentery on the stage of the microscope. Or he shaved off the papillary surface of the frog's tongue and observed the vessels in the base of the wound. Or the web of the foot may be used to which a mild irritant such as dilute acetic acid is applied. Whichever of these methods he employed, soon, as Cohnheim remarks, "a succession of appearances will be developed which are well calculated to fully engross your attention."

There may be a brief contraction of the vessels due to the stimulating effect on the vessel wall produced by the irritant when still weak in its action, but the first thing to attract attention is a dilatation of the exposed vessels, most marked in the arteries, then in the veins, and last of all in the capillaries. This paralytic dilatation is accompanied by a temporary acceleration of the blood stream, followed later by slowing. At this stage the vascular dilatation is very marked and innumerable capillaries come into view, because though previously empty they are now filled with blood, so that the active capillary bed is greatly increased and the vascularity of the part may actually be doubled. The increased vascularity is responsible for such cardinal signs as redness, swelling and heat. The slowing of the blood stream in the still dilated vessels becomes more and more marked, and if the action of the irritant is sufficiently intense there may be complete stasis or stoppage of the local circulation, with clotting (thrombosis) of the blood. The effect of the thrombosis is disastrous, for the tissues cannot survive when their blood supply is cut off, and death of the part (necrosis or gangrene) is certain. In the slower blood stream it now becomes possible to distinguish the individual corpuscles. It is then seen that a rearrangement of the formed elements of the blood has taken place. Under normal conditions the red and white cells flow intermingled in the central part of the vessel, forming an *axial stream* which is separated from the wall of the vessel by a clear *plasmatic zone* free from cells. In the veins of the inflamed part the leucocytes fall out of the axial stream and come to occupy the plasmatic zone. They tend to adhere to the vessel wall, and seem to drag themselves along with difficulty. In this way the inner wall of the vein becomes paved by an unbroken line of leucocytes without the admixture of a single red blood cell. This arrangement is spoken of as the *pavementing* of the leucocytes.

The vascular endothelium does not remain passive during this period of excessive activity. The lining cells become enlarged and proliferate, they assume a rounded form so as to project into the lumen of the vessel, and they exhibit amoeboid movement. In sections of inflamed tissue this swell-

ing of the endothelium is a striking feature (Fig. 34), and if the observer is fortunate he may detect evidence of cell division (mitosis).

The next step is the *emigration* or *diapedesis* of the leucocytes. The ground substance or cement of the swollen endothelial cells becomes loosened, the sharpness of outline of the individual elements of the vessel wall is lost, and its outer limit is nebulous. Through this protoplasmic sponge flows the cytoplasm of the polymorphonuclear leucocytes just as smoke floats through a keyhole. (Fig. 35). Numbers of red blood cells may follow in the wake of the leucocytes, but these numbers vary widely, depending on the nature of the irritant. When particularly numerous the inflammation is said to be hemorrhagic. It will be seen that the essence of inflammation, the central point of the whole process, is the increased permeability of the walls of the small veins and capillaries.



FIG. 34.—Swollen endothelial cells with leucocytes passing between them.  $\times 1300$ .

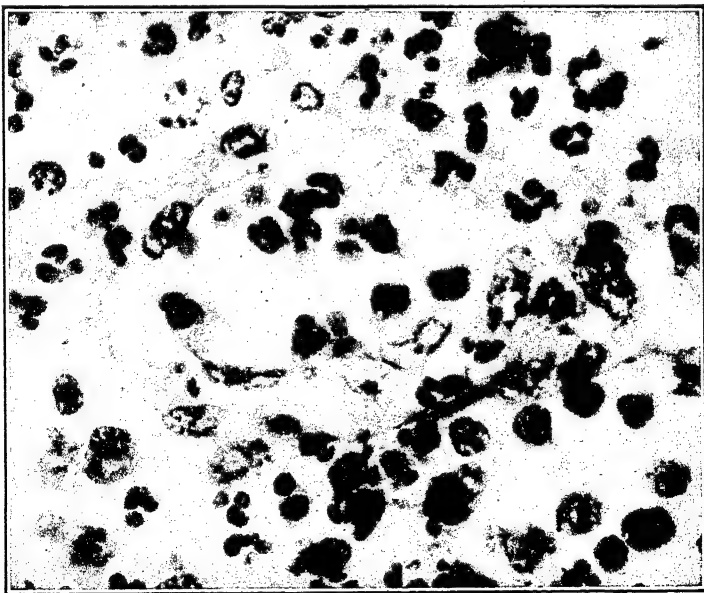


FIG. 35.—Separation of elements of vessel wall; emigration of leucocytes.  $\times 800$ .

The outward movement is not confined to the solid particles of the blood. The blood plasma also passes out into the tissues, the amount varying much with the nature of the irritant. In the tissues it may be responsible for much of the swelling, causing an inflammatory edema. The subject of the plasma in the tissues will be taken up when the inflammatory exudate is considered.

In inflammation there is not only an opening up of preëxisting capillaries but also a formation of new vascular channels. This is accompanied by new formation of lymphatic capillaries (Pullinger and Florey). An astonishingly rich plexus of lymphatics is formed by the end of ten days. These vessels are only visible when injected owing to the colorless nature of their contents. They disappear as healing occurs.

*The Influence of the Nervous System.*—The vascular changes, both dilatation and exudation, are influenced by nervous impulses. If in one ear of a rabbit the vasoconstrictor nerve be cut and in the other ear the vasodilator nerve, and inflammation of both ears be then produced by means of hot water, a marked difference in reaction on the two sides can be observed. In the ear where the constrictor fibers are cut hyperemia is marked and complete recovery ensues. In the ear where the dilator fibers are cut the vessels remain constricted, stasis soon develops, and there will be a considerable amount of necrosis of tissue. When the nerve to a part is divided the normal constrictor impulses are cut off, and inflammation develops much more rapidly than usual. In such a part the capillaries permit a greater emigration of leucocytes and a greater transudation of lymph through their walls.

It is evident that the more rapidly and completely a condition of hyperemia can be induced, the more satisfactory will be the inflammatory response, the less damage will be done, and the more complete will be the return to normal. This provides an explanation of the value of hot moist applications to an inflamed part. The fomentations act through the local vasodilator nerves, increasing the hyperemia, hastening the formation of an exudate, and limiting the spread of the infection. It is possible that there may be a liberation of acetylcholine at the nerve endings, and that this may produce a local action on the vessels.

**PHAGOCYTOSIS.**—A unicellular organism such as an amoeba shows to a marked degree the power of taking foreign particles into its body. The cell of which the organism is composed swallows or devours the particle. Hence the process is known as phagocytosis (*phagein*, to eat). The mechanism is that of amoeboid motion, the same by which the leucocytes pass through the vessel walls. The cytoplasm of the cell flows out in one or more processes or *pseudopodia*, which surround the particle and draw it within the body of the cell. Here it undergoes digestion, a vacuole being formed around it which contains a digestive ferment. If the particle can be dissolved and digested it gradually disappears; if not, it is discharged from the cell.

In vertebrates these cells are represented by the polymorphonuclear leucocytes of the blood and the large mononuclear phagocytes of the blood and of the tissues, those cells called by Metchnikoff the macrophages. The former engulf bacteria, both alive and dead. If a mixture of leucocytes

and bacteria is incubated and a film is then spread and stained, numbers of the bacteria will be seen lying within the leucocytes. (Fig. 36.) The macrophages devour dead cells, blood pigment, inorganic particles, etc. They are true scavengers. They may also engulf protozoal parasites. In acute inflammation the polymorphonuclears play the chief part in the early stages, the macrophages taking their place in the later stages. The two sets of cells react differently to different bacteria. Thus the mononuclears will not take up streptococci or gonococci which the polymorphonuclears readily devour, but they will take up tubercle bacilli or leprosy bacilli.

When foreign particles which cannot be digested have to be removed, such for instance as pieces of bone or cholesterol crystals, the macrophages fuse together so as to form *giant cells*. Such a foreign body giant cell is a cytoplasmic syncytium containing a large number of nuclei. In this form it seems to have greater phagocytic power than when the cells act singly. These cells are seen in various chronic inflammations such as tuberculosis and syphilis.

**THE MECHANISM OF THE VASCULAR PHENOMENA.**—The result of the vascular changes which have just been described is to bring both the solid and the fluid constituents of the blood from the interior to the exterior of the vessels, where they encounter the irritant responsible for the reaction. It has been said that the object of the exudate is to destroy and remove the irritant, and that the object of the vascular phenomena is the formation of the exudate. A teleological view of this kind is a mistake. There is nothing transcendental about the process, which is governed by purely physico-chemical laws and must not be looked upon as purposive in nature.

The varied changes of inflammation both in the vessel walls and in the blood and tissue cells are due to chemical stimuli produced at the site of irritation. The commonest of all irritants are bacteria, and these produce chemical substances which indirectly act upon the vessels. Even in aseptic inflammation caused by mechanical or thermal injuries there is destruction of tissue with the liberation of disintegration products which exert a similar action. An excellent account of the chemical side of inflammation will be found in Wells' *Chemical Pathology*.

The *vascular dilatation* which is so striking a feature is due to paralysis of the muscular fibers of the small arteries and veins. Krogh has shown that even the capillaries possess contractile power, and these vessels also are paralyzed. It is probable that paralysis of the vasoconstrictor nerves may play a part in the earliest stage of inflammation, but as the vascular changes are seen in tissue which has been completely separated from the

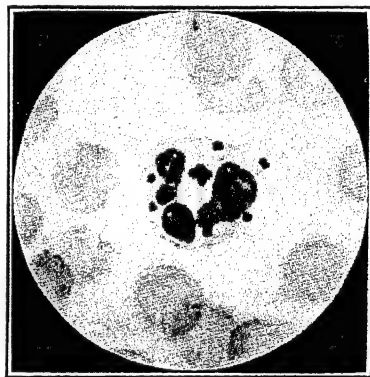


FIG. 36.—Polymorphonuclear leucocyte containing bacteria.  $\times 1250$ .

nervous system it is evident that the chief action is a direct one on the vessel wall.

Sir Thomas Lewis has shown that the vascular dilatation which follows firm stroking of the skin is due to the liberation of a histamine-like or "H"-substance. He suggests that in the tissue destruction of inflammation a similar substance is liberated and sets in motion the vascular mechanism. "The agent that alarms the garrison and mobilizes the first or vascular defenses is a chemical agent derived from the tissues. The perfection of this mechanism is such that the defense is organized immediately and at every threatened point; it is arranged and carried through locally, being independent of higher systems of control (nervous) and of distribution (cardiovascular)." (Lewis.)

The *escape of the blood plasma* is probably due to a number of factors. The capillary walls are injured by the toxins and are thus rendered more permeable. The osmotic pressure of the tissues is increased, due to the colloid proteins being broken down into crystalloid substances with a high osmotic pressure. This disturbance of the osmotic pressure causes the plasma to pass from the vessels into the tissues.

It is the *emigration of the leucocytes*, however, which has the greatest suggestion of purposiveness. They multiply in the bone-marrow and thus increase in number in the blood stream, they pass through the walls of the vessels and accumulate at the site of irritation, and they finally engulf and devour the bacteria by the process of phagocytosis to be described presently. These actions seem intelligent and volitional, but they can be explained on a physico-chemical basis. The force which not only draws the leucocytes out of the bloodvessels but causes them to move through the tissues is known as *chemotaxis*, and has been defined as "a directional response to a substance in the environment." (McCutcheon). It seems probable that the mechanism involved is a lowering of the surface tension on one side of the cell, as a result of which the cytoplasm flows by amoeboid movement in that direction.

Menkin has shown that a crystalline nitrogenous substance can be obtained from acute inflammatory exudates which increases capillary permeability and induces prompt leucocytic migration. For this reason he calls the substance *leucotaxine*. Moon and Tershakovec, however, point out that substances derived from damaged cells attract leucocytes into the area, in addition to causing hyperemia and edema. The injured cells issue their own call for help and thus mobilize the forces of defense long before the action of leucotaxine derived from the inflammatory exudate.

There is a negative as well as a positive chemotaxis. Such substances as quinine, alcohol, and lactic acid repel rather than attract the leucocytes. The result depends to some extent on the concentration of the material. If the solution is made sufficiently dilute the negative action is changed into a positive one. When bacteria are extremely virulent they cease to exercise any positive chemotactic power, and merely paralyze the leucocytes. If the two ears of a rabbit are inoculated with an attenuated and a virulent culture respectively, in the former there will be a great accumulation of leucocytes with very little fluid, while in the latter there will be an abundant effusion of fluid but hardly any leucocytes.

The various leucocytes show different degrees of response to chemotaxis. The polymorphonuclear leucocytes are the most readily affected. The lymphocytes are much less active probably because of the small amount of mobile cytoplasm which they contain. For this reason it seems likely that most of the cells of "small round cell" collections in chronic inflammation are derived from the tissues rather than from the blood. Of particular interest is the behavior of the white cells in an inflammatory focus in a patient with lymphatic leukemia. In this disease there may be 99 per cent of lymphocytes in the blood to 1 per cent of polymorphonuclears, and yet if an inflammatory blister of the skin is produced, the exudate consists of polymorphonuclear forms with hardly a single lymphocyte. The products of animal parasites attract the eosinophil leucocytes more than any other variety, so that these increase in number both in the blood and in the tissue affected.

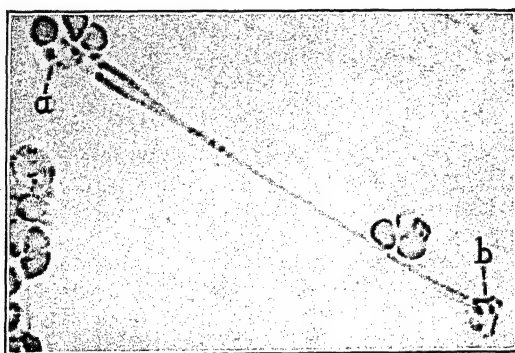


FIG. 37.—Photograph of living leucocyte showing stretching of cytoplasm: (a) portion of leucocyte containing 3 red cells attached to slide; (b) migrating portion. (Mudd and Mudd, *Jour. Gen. Physiology.*)

Let us now apply these general considerations to a given instance of inflammation. Bacteria gain entrance to the finger and produce chemical poisons. Even if the irritant is non-bacterial the tissues are injured, and the chemical products of cellular disintegration are liberated. These chemical substances act upon the walls of the vessels producing the paralytic dilatation and the swelling of the endothelium already described. They pass through the walls of the capillaries at the thinnest parts, probably between the endothelial cells, and exert their chemotactic influence on the leucocytes flowing past. They lower the surface tension of the leucocytes on the side nearest the capillary wall, so that they move from the center of the stream over to the wall, to which they tend to adhere in a sticky manner. Still under the chemotactic influence, the leucocytes push out pseudopodia between the endothelial cells, and finally pass through the vessel wall. They then move through the tissue spaces to the site of the irritant. The chemotactic substances are carried by the blood stream to the bone-marrow, where they repeat the process on the leucocytes stored there, lowering their surface tension on one side and drawing them into the

blood stream. In this way a leucocytosis is produced, the supply being kept up by proliferation of the parent cells of the leucocytes, the myelocytes of the marrow. As long as the blood contains more chemotactic substances than the marrow, the leucocytosis will increase.

Phagocytosis may be regarded as a special result of the process which has just been described. The leucocyte merely continues its onward movement until it flows around the particle and engulfs it. Stuart Mudd

and his associates have shown that phagocytosis involves the spreading of the leucocyte over the surface of the particle until the latter is completely enclosed; the capacity of spreading is the principal factor. (Fig. 37.) The deposition of serum protein on the surface of the particle greatly increases this power. When leucocytes are examined at the interface of an oil-water mixture, their remarkable deformability at once becomes evident. This appears to depend on the wetting properties of the leucocytes; they are hydrophilic. Red blood cells, on the other hand, are hydrophobic and exhibit no deformability. (Mudd and Mudd.)



FIG. 38.—Leucocytes collected at point of bifurcation of a dilated vessel.  $\times 200$ .

**The Inflammatory Exudate.**—The exudate which collects at the site of irritation is partly derived from the blood (hematogenous), partly from the tissues (histogenous). The various forms of leucocytes of the blood migrate through the vessel walls; the blood plasma also passes out, and gives rise to the formation of fibrin; the wandering cells of the tissues accumulate at the site of irritation. These three constitute the inflammatory exudate. Red blood

cells may be present in varying degree, but have no functional part to play. Let us now examine these various elements in greater detail.

**THE POLYMORPHONUCLEAR LEUCOCYTE.**—These cells are the active agents in acute inflammation, especially in its earlier stages. They are called forth in particular by the pyogenic group of bacteria, and form the chief constituent of pus. The ordinary pus cell is a polymorphonuclear leucocyte. The great increase in the number of leucocytes in the blood which occurs during inflammation is an increase of the polymorphonuclears. In sections of inflamed tissue the vessels may be packed with these leucocytes. They are attracted not only by bacteria but also by their toxins, as can be shown by the experimental injection of a toxin freed from the microorganisms by



which it is produced. The cells collect in great numbers around the dilated vessels (Fig. 38), and they pass through the tissue spaces by their amoeboid movement. They are actively amoeboid and actively phagocytic. Their power of movement is remarkable, but they cannot swim through fluid with any degree of effectiveness. They must have a framework on which to crawl. It is fibrin which provides the interlacing pathways that bridge across the fluid-distended spaces on which the leucocytes can move. The phagocytic power is shown towards bacteria rather than to dead and disintegrating cells. They form the first line of defense of the body against pyogenic bacteria, and constitute the microphages of Metchnikoff. Having devoured the bacteria they secrete a digestive ferment which brings about solution of the bacterial bodies. Large numbers of the leucocytes are killed by the bacterial toxins, but even in their death they serve the body, for on disintegrating they liberate a proteolytic ferment which dissolves the dead tissue, and thus hastens the process of ultimate recovery. This ferment has a similar action on fibrin, and tends to prevent its formation. In a fresh exudate the cell outline is sharp and the nucleus distinct, but as degeneration proceeds the cytoplasm becomes granular, the outline indistinct, and the nucleus eventually disappears. Many of the cells which survive pass back into the lymphatics and bloodvessels and reënter the general circulation.

**THE EOSINOPHIL LEUCOCYTE.**—The eosinophils of the blood are few in number, constituting only from 2 to 4 per cent of the total white count. They appear early in the inflammatory exudate, and may disappear entirely from the blood. A marked increase in the number of eosinophils in the blood (eosinophilia) is characteristic of infection by many animal parasites. Large numbers of these cells are found in the tissue in which the parasite is lodged. In bronchial asthma the mucosa of the bronchi is often crowded with eosinophils. In both of these instances the eosinophilia may be a reaction against a foreign protein. A marked tissue eosinophilia is sometimes seen in appendicitis in the subacute or chronic stage. Eosinophils are frequently present in the lesions in the lymph nodes in Hodgkin's disease. In these latter instances the cells may be derived from the tissues rather than from the blood. Dalton points out that eosinophilia, both in the tissue and the blood, is a constant accompaniment of the allergic reaction. These cells may serve as a factor in causing the allergic response. He suggests that the antibodies rather than the antigen may be responsible for the eosinophilia, which in post-infection states rises with the rise of antibody titer. Eosinophils on breaking down release histamine, with resulting increase of capillary permeability and outpouring of more antibodies and neutralization of the antigen. Clinical manifestations of allergy may result. In support of the idea that there is a relationship between the eosinophils and histamine is the fact that the eosinophilia which follows injection of extracts of the worm *Ascaris* is completely prevented by the use of antihistamine drugs.

It is common knowledge that the administration of ACTH or cortisone produces a rapid and remarkable disappearance of the eosinophils of the blood, so much so that this reaction is used as an indication of the response of the body to these hormones.

**THE MAST CELL.**—This is a cell with coarse basophilic granules in the cytoplasm, and an indented or polymorphonuclear nucleus. It is the basophil leucocyte of the blood, present normally in very small numbers, and is also found in the tissues. These cells are observed in mild subacute inflammations, but they show a marked tendency to disintegrate, so that the granules alone may be seen. Mast cells stain metachromatically with toluidin blue, and, as Jorpes has pointed out, tissues which are rich in heparin stain in a similar manner. Examples are the subintimal tissue of bloodvessels, and subpleural and subperitoneal connective tissue. It is reasonable to suggest that mast cells are concerned with the production of heparin.

**THE LYMPHOCYTE.**—In chronic inflammation and in the later stages of acute inflammation the lymphocyte may be the main cell of the exudate. The cells of such collections are often called by the non-committal name of "small round cells." Some of these cells no doubt are derived from the tissues, but for the most part they come from the blood. "The complete ignorance of the function of the lymphocyte is one of the most humiliating and disgraceful gaps of all medical knowledge. They phagocytose neither bacteria nor other particulate matter. Congregated often in the more peripheral parts of the lesion, they have the appearance of phlegmatic spectators passively watching the turbulent activities of the phagocytes." (Rich). It is now known that antibody formation occurs largely in lymph nodes (McMaster and Hudack), and there is evidence to suggest that the lymphocytes are the cells which produce the antibodies, although some workers believe that these cells merely store and carry the antibodies. The release of the gamma globulin from the cytoplasm of lymphocytes is under the control of the pituitary (ACTH) and more directly of the adrenal cortex (cortisone). These hormones control the rate of dissolution of lymphocytes and lymphoid tissue, from one-third to one-half of the circulating lymphocytes disappearing in the course of an hour after administration of the hormone. Maximow believed that lymphocytes developed into macrophages, because in tissue culture he observed them acquiring a large amount of cytoplasm and the power of phagocytosis. Pathologists have not observed this transformation in tissue sections, but Kolouch has shown that it can occur rapidly. By injecting egg albumin into the subcutaneous tissue of rabbits and examining imprints of the exudate at short intervals he was able to demonstrate the hour by hour development of lymphocytes into phagocytic macrophages. The change was completed in less than eighteen hours. Kolouch's photomicrographs are very convincing. In chronic inflammation the lymphocytes remain for the most part as small round cells; in acute inflammation they appear to change into macrophages.

Some interesting facts relating to the role of the lymphocyte will be found in Ehrlich's excellent review. Normally the intermediate lymph (which has passed through lymphoid tissue) contains 10 times as many lymphocytes as does the peripheral lymph. In a dog weighing 10 kilos, 5 billion lymphocytes are poured out of the thoracic duct into the venous blood every day. As the circulating blood contains only  $2\frac{1}{2}$  billions, it would appear that the lymphocytes are replaced twice a day. In the rabbit they are replaced 5 times a day. The life cycle of the lymphocyte seems to be completed in a few days. It is possible that the germinal centers

of the nodes may be the graveyard rather than the birthplace of the lymphocytes. As the lymphocytes produce the normal gamma globulin it is evident how important a source of immune bodies they represent.

**THE PLASMA CELL.**—Two points regarding this cell are deserving of note. (1) It is never present in the normal blood, and (2) its form is so characteristic that it is readily recognized. (Fig. 39.) The plasma cell is larger than the lymphocyte with more abundant cytoplasm; it is not quite round but slightly polygonal in outline, and the nucleus is eccentric so that the cell has a lop-sided appearance. The chromatin is collected in small masses around the periphery of the nucleus like the figures on a clock-face. This clock-face arrangement of chromatin is only seen in sections, not in smears of the blood or bone marrow. It is apparently an artifact due to fixation. The cytoplasm is intensely basophilic, and presents a clear space on the side of the nucleus which faces the center of the cell. The plasma cell does not appear to be a distinct species of cell like the lymphocyte or fibroblast, but rather a functional stage of various multipotent cells of connective tissue which undergo cytomorphic changes in cytoplasm and nucleus ending in the development of a plasma cell. The principal cell of origin is the lymphocyte, but it may arise from various members of the reticuloendothelial system. The plasma cell has been called the key to allergic processes. Hypersensitivity, both experimental and clinical, is associated with the development of plasma cells. The cycle of maturation is initiated by anaphylactic shock. The cytoplasm appears to secrete antibodies (globulins.) There is an invariable relationship between plasmacytosis and hyperglobulinemia, which is an important feature of many immunologic processes. Plasma cells in the tissues are increased in long-continued infections with marked immunological response such as syphilis and rheumatoid arthritis, in hypersensitivity states, and in multiple myeloma where they seem to be related to the presence of Bence-Jones protein in the urine.

**THE MACROPHAGE.**—Many names have been given to the large mononucleated cells which play so important a part in the later stages of acute inflammation and in some types of chronic inflammation. Amongst such names may be mentioned polyblasts (Maximow), clasmatocytes (Ranvier), adventitial cells (Marchand), large mononuclears, monocytes, histiocytes (Aschoff), and macrophages (Metchnikoff). Some of these names reflect

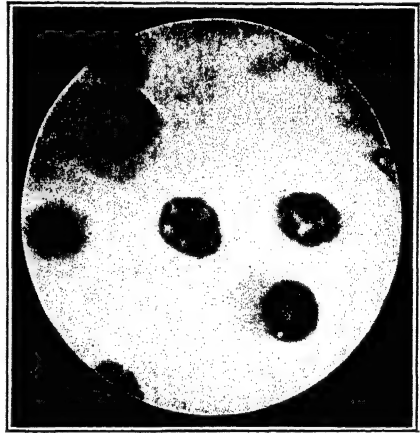


FIG. 39.—Two plasma cells showing polygonal shape and eccentricity of nucleus. The other two cells in the center are lymphocytes.  $\times 1600$ .

doubt as to their origin. It is probably twofold: from the blood and from the tissues.

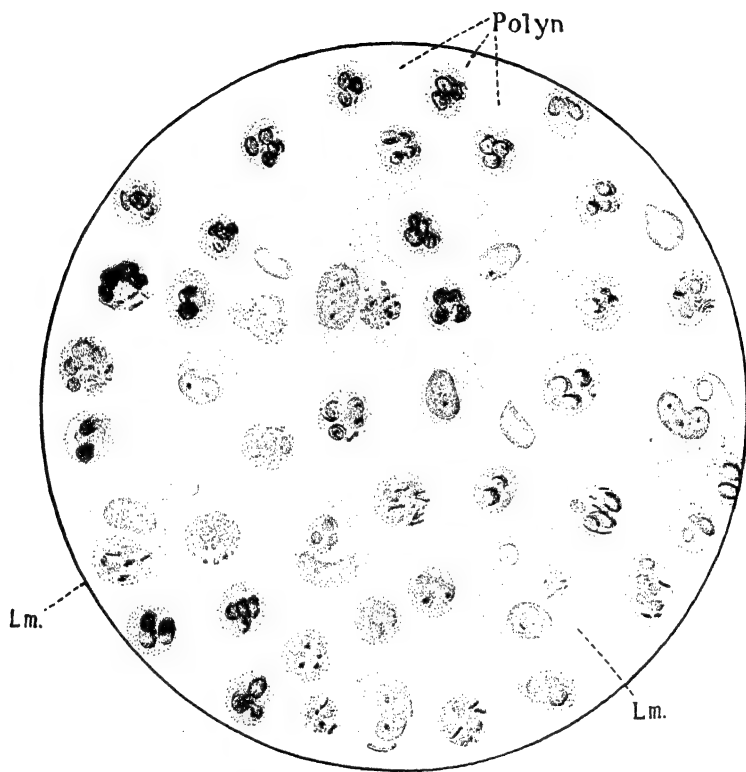
In the discussion on the lymphocyte it was pointed out that there is good reason to believe that many lymphocytes derived from the blood become converted into macrophages at the site of inflammation by increase in the cytoplasm and enlargement of the nucleus. Ebert and Florey, using Clark's transparent observation chamber in the rabbit's ear and moving picture technic, observed monocytes marked by vital dye and traced their passage through capillary walls into the tissues, where they became converted into macrophages.

It is probable that the bulk of the macrophages are histogenous in origin, particularly from the reticulo-endothelial system. They are derived not only from cells lining blood sinuses, such as the Kupffer cells of the liver, but from the tissue cells of that system known as histiocytes. In addition to the fixed cells there are nomadic mesodermal cells which have no fixed abode, but wander through the tissues by virtue of their amoeboid powers. The distinction between the fixed and the wandering cells can be most readily realized by studying tissue cultures, and can be demonstrated in a dramatic manner by projecting a moving picture of the culture on the screen, when the actively amoeboid and actively phagocytic nature of these cells becomes vividly apparent.

MacCallum has given an unsurpassed description of such a picture. "The connective tissue cells grow out majestically and smoothly from the margin of the field, crossing and interlacing until a firm new structure is formed. Among these cells one may see others of quite different aspect worming their way with no thought of building. Arrived at the margin where they escape from the entanglement of these more serious fibroblasts, they show their true characters. Some are polymorphonuclear leucocytes, and they hop about within a limited area in a sort of ecstatic frenzy, evidently throwing out and retracting pseudopods at a great rate. Then there are lymphocytes which move humbly, like slugs crawling only a little way with head to the ground. But also there are macrophages which reach out great arms, perhaps in two or more directions, and at the end of these arms there is a flourish of clear protoplasm with outflung streamers that wave and search about for whatever can be seized, or else the whole advancing margin of the cell flows out and comes back like a wave, sucking in any particle that comes in its way." In the fixed and stained tissue of a microscopic preparation the cells lose all this vivid character, and appear as large pale rounded bodies with a vesicular nucleus and abundant cytoplasm. The marginal portion of the cytoplasm when viewed with dark-field illumination is seen to be an extremely delicate membrane, which undulates incessantly like a delicate silk veil when blown by the wind. It is from this membrane that the pseudopods are formed, and it appears to play the part of the spider's web which envelops foreign particles in its voluminous folds.

It is these cells which form the scavenger cells of ordinary inflammation, the epithelioid cells of tuberculosis and syphilis, the compound granular corpuscles which surround an area of brain softening, the heart failure cells which take up blood pigment in the lung when the heart is failing,

# PLATE III



Film Made from Peritoneal Fluid in Case of Peritonitis set up by Inoculating *B. Coli* Twenty-four Hours Previously into the Abdominal Cavity of a Rabbit. (Beattie.)

*Polyn.*, Polynuclear leukocytes, many containing bacilli; *Lm.*, large hyaline mononuclear cells, many acting as phagocytes for polynuclear cells, red corpuscles, etc.

the large phagocytes which form a zone around a chronic abscess, and finally, when the utmost in phagocytic action is needed, they fuse together to form giant cells. Their amœboid and phagocytic character is better seen in smears made from inflammatory exudates and immediately fixed (Plate III) than in sections of inflamed tissue, in which the pseudopodia are retracted and the outline becomes rounded.

**GIANT CELLS.**—When the individual macrophages are unable to deal with particles to be removed, they fuse together and form multinucleated giant cells. Excellent examples of giant cell formation can be seen around a foreign body such as a fragment of bone, a piece of ligature, a crystal of cholesterol, or even a splinter of wood. (Fig. 40.) For this reason the cells are called foreign body giant cells. They may contain enormous numbers

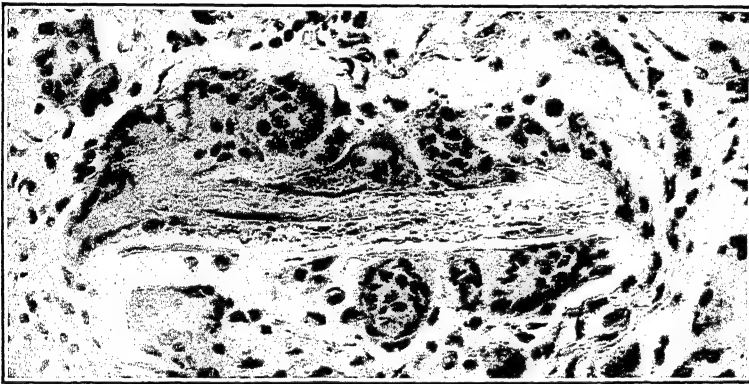


FIG. 40.—Sliver of wood surrounded by giant cells.  $\times 300$ .



FIG. 41

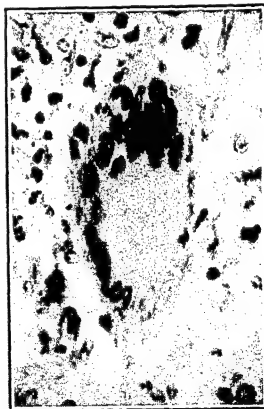


FIG. 42

FIGS. 41 and 42.—Types of giant cells

FIG. 41.—Tumor giant cell with several large nuclei.  $\times 400$ .

FIG. 42.—Foreign body giant cell with a large number of smaller nuclei arranged around the periphery and at one pole.  $\times 700$ .

of nuclei, which cannot all be seen in one section, since the cell is spherical.

It must not be supposed from this brief summary that the subject of giant-cell formation is as simple as it sounds. Haythorn's excellent review of the whole subject contains 391 references. Three great classes of giant cells must be distinguished: (1) tumor giant cells, (2) foreign body giant cells, (3) a miscellaneous group. (Figs. 41 and 42.)

*Tumor giant cells* are best seen in osteogenic sarcoma of bone, in glioblastoma multiforme (a malignant tumor of the neuroglia), in rhabdomyosarcoma (a malignant tumor of muscle), and in primary carcinoma of the liver. They are large cells, and have one or several nuclei, but these are never very numerous. The nuclei are often hyperchromatic so that they stain very darkly, and may vary considerably in size and shape, so that the cell has a more atypical neoplastic appearance than the Langhans' type of cell. The genesis is also different, for tumor giant cells are formed by the nucleus of the cell dividing while the body of the cell fails to divide. These giant cells are not derived from the macrophages but from the cells of the tumor, whether connective tissue or epithelial in nature.

The *foreign body giant cell* is larger than an ordinary cell and may be of enormous size; it contains numerous nuclei, sometimes as many as 50 or 100. The nuclei are regular in size and seldom large. In the ordinary type of giant cell engaged in removal of a foreign body, the nuclei are scattered through the cytoplasm. In the giant cells so characteristic of tuberculosis, also known as the Langhans' type of giant cell, the nuclei tend to be arranged around the periphery or are collected at one or both poles of the cell.

Foreign body giant cells may be found in a great variety of conditions. Of these the commonest is tuberculosis, but it is a great mistake to jump to the conclusion that a lesion containing giant cells must be tuberculous. They are found in other chronic destructive inflammations such as syphilis, leprosy, actinomycosis, and blastomycosis. In leprosy the cells may be crowded with bacilli (lepra cells), and in tuberculosis they may contain a smaller number of tubercle bacilli. Any destructive lesion of bone may contain giant cells. They form the most striking feature of the giant-cell tumor of bone. Giant cells may be found at the site of old hemorrhages, but they are more often associated with attempted removal of cholesterol crystals. I have seen examples of this in atheroma of the aorta. The lesions of traumatic fat necrosis often show numerous giant cells, and are easily mistaken for the lesions of tuberculosis.

*Asteroid inclusions* or radial inclusions are observed in giant cells in tubercle-like formations in a variety of conditions. These are most characteristically seen in sarcoidosis, but are also found in subcutaneous tissues containing paraffin, in the wall of dermoid cysts, in old hemorrhages, etc. They have been observed in the liver, spleen and lymph nodes. Hirsch, from an exhaustive examination of human and experimental material, came to the conclusion that the star-like inclusions represent crystalline forms of fat separated from an oil system containing cholesterol. Chemical changes take place in the composition of the crystals in the tissues so that they become insoluble in fat solvents. Cunningham believes that they are organic protein structures present in many foreign body reactions. They are best stained with phosphotungstic acid hematoxylin.

In addition to the two great groups of tumor giant cells and foreign body giant cells, a *third miscellaneous group* may be recognized. In certain conditions of continued irritation the mesodermal cells become larger and may contain several nuclei. The large Aschoff cells of the rheumatic nodule offer one example. Another is the Reed-Sternberg cell of Hodgkin's disease.

THE LYMPH OF THE EXUDATE.—Under normal conditions a certain amount of blood plasma passes through the vessel walls into the tissue spaces where it constitutes the lymph. From these spaces it is absorbed into the lymphatics, and passes *via* the thoracic duct back into the blood stream. There is thus a continuous flow from the blood into the tissues, but the fluid is absorbed at an equal rate so that it does not accumulate in the tissue spaces.

The lymph which escapes from the vessels is not the same as the plasma which remains; it is thinner and contains much less protein, owing to the selective action of the vascular endothelium.

In inflammation the outward flow is enormously increased. By inserting a cannula into one of the chief lymphatics of the leg and then producing inflammation of the foot by immersing it in hot water, Cohnheim was able to show that the flow of lymph might be increased to eight times the normal. Drinker and his associates have amplified these observations. They found that the lymph flow in the inflamed part showed an extraordinary increase, and that the subcutaneous lymphatics were so greatly dilated that they could be injected with ease. It is evident that the lymphatics do not collapse as the result of pressure of the fluid in the tissues, as is sometimes supposed. The normal lymph pressure in the leg of a dog is too low to be measured, but in sterile inflammation it rose to 120 cm. of lymph. The increased lymph flow lasted as long as twenty-four hours. The production of fluid is so great that it cannot be carried away by the lymphatics, and therefore accumulates in the tissue spaces. Here it gives rise to inflammatory edema, which is the chief cause of the swelling of the part in acute inflammation. The lymphatic channels tend to become blocked with the inflammatory products; this increases the accumulation in the tissues. Inflammation of the lymphatics (lymphangitis) will still further aggravate the condition.

The principal factors in the production of inflammatory edema are changes in the capillary wall and increased osmotic pressure in the tissues.

The dispute regarding the filtration and secretion theories of the production of lymph must be left to the physiologists. We may take refuge in that non-committal term, the *permeability of the capillaries*. This is greatly increased by the action of the products of irritation on the vascular endothelium, so that the plasma is no longer held back within the vessels. Not only is the amount of lymph which escapes greatly increased; its quality is also changed. Normal lymph usually contains less than 1 per cent of protein, whereas in inflammation the lymph may contain as much as 8 per cent.

Of much greater importance is the *increased osmotic pressure* of the tissue fluids at the site of inflammation, which is a far more powerful force than the pressure inside the vessels. Early in the inflammatory process as the result of tissue disintegration metabolic products are liberated, for



the most part acid in reaction, and these so raise the osmotic pressure that fluid is drawn from the vessels to dilute them.

The amount of the fluid exudate varies greatly, depending on two main factors, the irritant and the site. (1) The bite of a mosquito and the sting of a nettle are examples of irritants which cause a marked outpouring of fluid. In a blister the exudate is almost entirely serous. Influenzal pneumonia is characterized by an extreme degree of inflammatory edema in the pulmonary alveoli. (2) The more open the tissue, the greater will be the exudate. It is most marked in serous sacs (pleurisy, peritonitis). In loose cellular tissues the fluid may be abundant. It may separate the muscle fibers of the appendix in acute appendicitis. (Fig. 43.) In such dense structures as bone the amount is negligible.

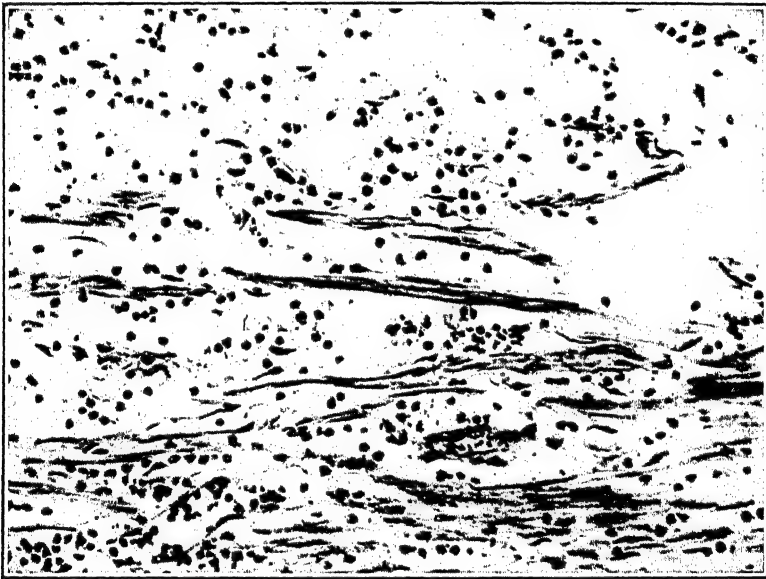


FIG. 43.—Muscle fibers of appendix widely separated by fluid exudate.  $\times 200$ .

*Fibrin formation* is intimately associated with the inflammatory lymph. The fibrinogen of the plasma passes out with the lymph, and this is acted on by the thrombin liberated by the disintegration of the polymorphonuclear leucocytes with the production of fibrin. This takes the form of a series of fine threads interlacing with one another. (Fig. 44.) The amount of fibrin varies with the irritant and the location, just as does the amount of lymph. Some bacteria such as the pneumococcus and the diphtheria bacillus excite an abundant formation of fibrin. Much fibrin is formed on serous surfaces such as the pleura and the peritoneum. Proteolytic ferments liberated by the leucocytes tend to prevent its formation, so that in an abscess crowded with pus cells no fibrin will be formed. The fibrin plays an important part in the process of healing, acting as a temporary scaffold on which the new tissue is built up. It may serve as a barrier against spread of the

infection, so that in pneumonia the pneumococci do not readily pass from the lung into the pleural cavity. An offset to these advantages is the fact that adhesions take their origin in the fibrin. Such adhesions are of value at first for they serve to localize the inflammation as in the case of an inflamed appendix. Later they may exact a penalty by undergoing contraction and thus gravely interfering with the function of the part affected.

**RELATION OF THE LESIONS TO THE CARDINAL SIGNS.**—It now becomes a simple matter to picture the pathological basis of the cardinal signs of inflammation. The *heat* is due to the increased amount of blood flowing through the part. The *redness* is also caused by the local hyperemia. The *swelling* is to be attributed in part to the vascular dilatation, but much more to the accumulation of exudate in the tissues. The chief constituent

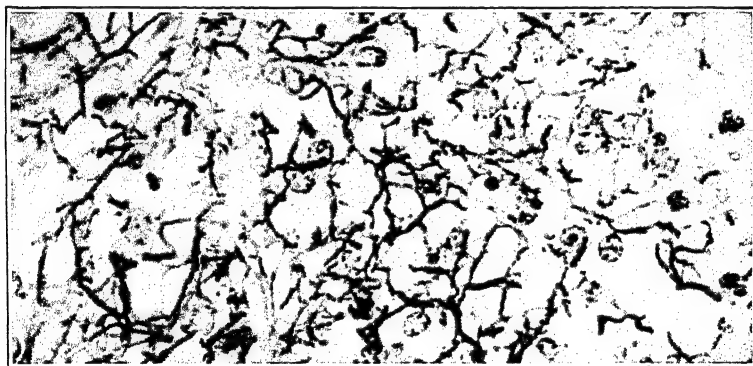


FIG. 44.—Exudate consisting mainly of fibrin.  $\times 600$ .

of the exudate responsible for the swelling is the lymph, the accumulation of which leads to inflammatory edema. There may be marked enlargement of an inflamed appendix, even though the cellular exudate is slight. The *pain* is caused by pressure on nerve endings. If the tension is great, as in a dense structure like bone, the pain will be severe. Stretching of a serous membrane rich in nerves will also cause much pain. *Loss of function*, varying in degree, is partly due to pain, partly to destruction of tissue.

**The Tissue Changes in Inflammation.**—The vascular phenomena and the formation of an exudate do not constitute the whole pathology of inflammation. There are also tissue changes. These may be of two types, (1) degenerative and (2) proliferative. If the irritant is intense, the effect is degeneration and destruction. If it is mild it acts as a stimulant, and the effect is proliferation. Growth will either be impaired or enhanced, the result depending on the intensity of the irritant. At the center of the inflammatory area the action of the irritant is severe, so that degeneration predominates; at the periphery the action is mild, so that the tissue may be stimulated to proliferate. This part of the inflammatory process is known as repair or healing.

The bacterial toxins poison the tissues of the inflamed part, leading either to degeneration or death (*necrosis*). Both of these processes have been discussed in the chapter on Degenerations. The two most common degenerations are *albuminous degeneration* or cloudy swelling and *fatty degeneration*. If either of these is carried too far the affected tissue will die and become necrosed. Should thrombosis of the vessels occur, necrosis will be hastened, as the tissues have lost their food supply. In addition to the bacterial toxins, the proteolytic ferments liberated by the broken-down leucocytes play an important part in the destructive processes, although they are unable to act on living cells. These ferments produce liquefaction of the dead tissues. The result is the formation of the fluid known as *pus*. It must not be supposed that every inflammation goes on to the formation of pus, and so becomes *purulent* in type. Some bacteria are pyogenic or pus-producing. Most of the pathogenic cocci are in this class and many bacilli. But some bacilli, such as the tubercle bacillus, lead to a proliferative reaction with little or no attempt at pus formation. Even the pyogenic cocci when few in number or of mild virulence may fail to produce a purulent inflammation. Large numbers of leucocytes are necessary for the formation of pus. If the exudate consists mainly of lymph or of fibrin, not sufficient leucocytes are present to produce the liquefaction which is necessary for pus formation. The serum contains an antibody which tends to inhibit the proteolytic enzyme of the leucocytes, so that in serous exudates there will be no autolysis. The leucocytes of some animals, such as the rabbit, contain but little enzyme; such animals usually fail to produce liquid pus. Living cells are not affected by digestive enzymes. Thus in lobar pneumonia the dead cells of the exudate undergo autolysis (resolution), but the living walls of the alveoli are left intact.

**INFLAMMATION OF SEROUS MEMBRANES.**—Inflammation of the pericardium, pleura, peritoneum, etc., is usually serofibrinous in type, *i. e.*, the exudate in the cavity is serous, but fibrin produced by coagulation of the exudate is laid down on the smooth surface of the membrane, covering it with a sticky, shaggy exudate or in milder cases merely robbing it of its normal sheen and imparting to it a frosted or ground-glass appearance. Microscopically the exudate consists mainly of fibrin, with a varying number of polymorphonuclears and some serum. As a result of the relative absence of pus cells from which the proteolytic ferments of inflammation are derived, the fibrinous exudate is not removed by autolysis. Instead, it undergoes the process known as *organization* which will be studied in connection with repair. New fibroblasts grow into the exudate and remove it in part or whole. If some of the exudate remains it is converted into dense fibrous tissue. If the two serous surfaces are stuck together by the exudate, as is often the case, the invasion of fibroblasts will sew the surfaces together at this point with permanent *adhesions*.

**SUPPURATION.**—If the dead tissue in an inflamed area undergoes softening and liquefaction the process is known as suppuration and the fluid formed is pus. This is the method by which the dead material is removed from the body. There are three requisites for suppuration: (1) necrosis; (2) the presence of sufficient leucocytes; (3) digestion of the dead material by proteolytic ferments. If any one of these is absent suppuration will not

occur. Anything which will produce both positive chemotaxis and necrosis will produce suppuration. Not only pyogenic bacteria and their toxins, but aseptic irritants such as turpentine and croton oil will cause typical suppuration. *The presence of leucocytes does not constitute suppuration.* The tissues may be crowded with polymorphonuclear leucocytes, but suppuration and pus formation need not be present. (Fig. 45.)

The digestive ferments are produced mainly by the leucocytes, and to a lesser extent by the necrosed tissue cells and the infecting bacteria. The part played by the leucocytes is readily shown by testing the action of pus on fibrin or egg albumen. This is easily dissolved by pus or purulent sputum, whereas non-purulent sputum has no effect. The action of the protease

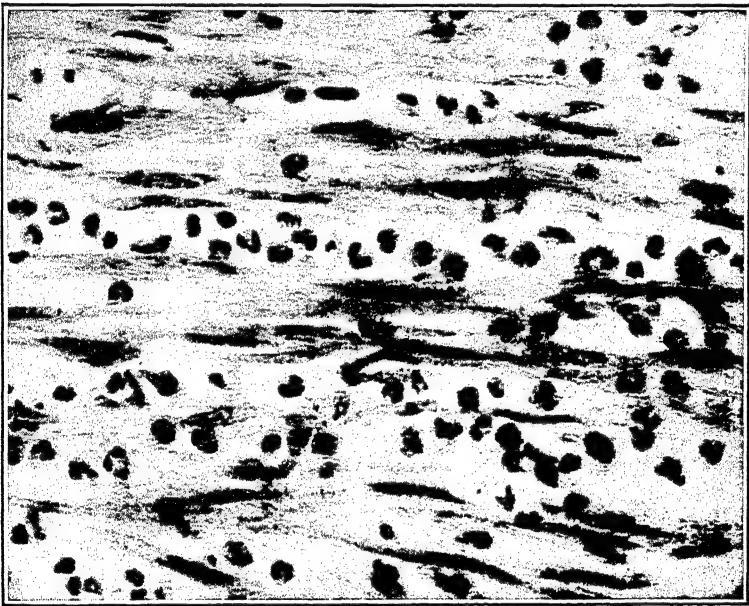


FIG. 45.—Muscle fibers of appendix separated by leucocytes but without suppuration.  
× 500.

of the leucocytes tends to be inhibited by the antienzymes of the serum. On this account, if the exudate be rich in serum and poor in leucocytes, no liquefaction and suppuration will occur. Drainage of the serum by removal of the antienzymes may lead to liquefaction and removal of the dead tissue. In some animals such as the rabbit the leucocytes are poor in protease and the serum is rich in antienzymes. Opie has shown that in such an animal infection with the ordinary pyogenic cocci does not result in the formation of pus. The antienzymes appear to be of lipid character, such as unsaturated fatty acids. Tuberculous caseous material is rich in unsaturated fatty acids and therefore resists liquefaction. The toxins of the tubercle bacillus appear also to destroy the autolytic ferments. Another reason why the ordinary tuberculous lesion does not suppurate is that it does

not contain leucocytes. If secondary infection occurs, or even if leucocytes are attracted to the part by the injection of iodoform, liquefaction and suppuration will soon follow.

*Pus* is the fluid product of suppuration. It is alkaline in reaction and usually yellowish in color. It consists of pus cells and pus serum, but in addition it contains the débris of tissue destruction and bacteria living or dead. The pus cells are leucocytes, for the most part polymorphonuclear in type. If the exudate is fresh as in the discharge from a recent gonorrhea, the details are sharp and the cells are well preserved. If the exudate is old, all details may be lost.

The *pus serum* is inflammatory lymph to which are added the products of cell disintegration. It does not coagulate, because the fibrinogen of the blood plasma is destroyed by the enzymes of the leucocytes. It is for this reason that the exudate of a serous pleurisy when removed from the body will clot into a jelly-like mass, while the much thicker exudate of a purulent pleurisy (empyema) will remain uncoagulated.

An *abscess* is an example of localized suppuration. The inflammation is limited to one area, and as the irritant is a pyogenic one, pus is produced. When staphylococci lodge in the kidney, an acute inflammatory reaction results, the cells in the center of the focus are killed, and are liquefied by the proteolytic enzymes. (Fig. 46.) In this way a cavity is produced which contains

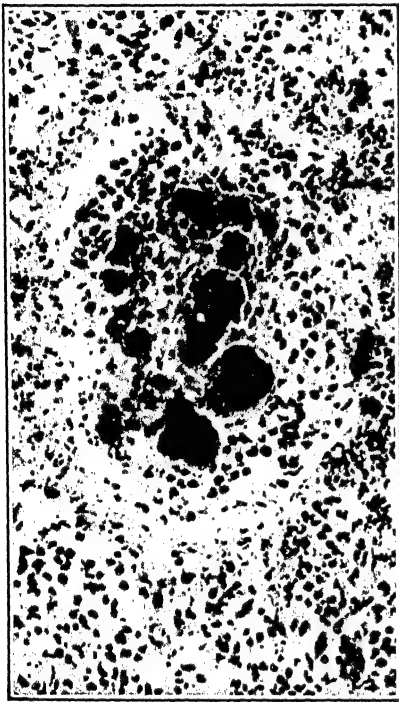


FIG. 46.—Abscess of kidney showing dark masses of bacteria and destruction of tissue.  $\times 275$ .

fluid pus. The wall of the abscess cavity consists of damaged but still living tissues. It is here that the struggle goes on to limit the spread of the infection. (Fig. 47.) This limiting zone is crowded with polymorphonuclear leucocytes and with macrophages filled with débris. Pus cells are continually discharged from this zone into the abscess, so that it is called the *pyogenic membrane*. If the abscess is chronic, or if the infection is dying out, the macrophages will greatly outnumber the polymorphonuclears. Further out the tissue becomes more normal.

If the infection continues active, more and more material is added to the abscess, so that the pressure within it rises. It therefore tends to extend or "point" in the direction of least resistance. In the kidney it may discharge into the renal pelvis or on to the surface of the kidney. If the

abscess enters a muscle sheath such as that of the psoas it may trek along it for a considerable distance.

The path formed by an abscess in its effort to discharge on a free surface is known as a *sinus*. Should the abscess discharge simultaneously on to both a skin and a mucous surface, the path which connects these surfaces is called a *fistula*. If the mucous surface is in the bowel, feces will be discharged on the skin, and the fistula is a *fecal fistula*. A good example is the abscess which may form when an inflamed appendix ruptures, and which may eventually discharge both into the bowel and on to the abdominal wall. When an abscess reaches a surface, either skin or mucous membrane, the overlying tissue becomes necrosed, forming a *slough*, and when the slough is discharged an open sore or *ulcer* is produced. This is the usual fate of an abscess. An ulcer, which is an open sore, an interruption of surface continuity of skin or mucous membrane with accompanying inflammation, is, of course, frequently produced by injurious agents acting directly on the surface.

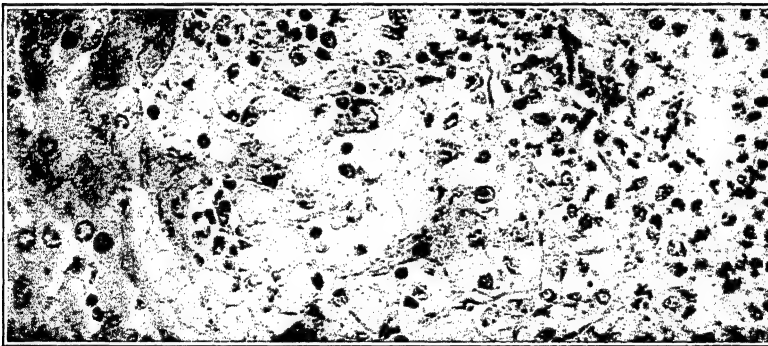


FIG. 47.—Wall of abscess in liver. At the left the liver cells are comparatively uninjured. At the right there is an acute inflammatory exudate.  $\times 300$ .

An acute inflammatory lesion which discharges on the surface generally heals quickly. Such a healing ulcer is called a *healthy ulcer*. Its floor is covered by pink granulations composed of the vascular connective tissue known as *granulation tissue*, any discharge which comes from it is slight and contains only a few pus cells, the edges are sloping and are bordered by a bluish-white line of ingrowing epithelium, and the surrounding parts are not inflamed. An ulcer may fail to heal and be *unhealthy* because of continued infection or defective circulation in the part. In such an ulcer the base is bathed with pus, the edges are ragged owing to continued tissue destruction, the epithelium shows no sign of covering the ulcer, the surrounding parts are inflamed and edematous or may be hard and sclerotic from fibroblastic proliferation. (Fig. 48.)

A *boil* is an abscess of a hair follicle or a sebaceous gland, caused by the *Staphylococcus aureus* which has penetrated the opening of a duct, owing it may be to repeated friction, so that it is commonest on the buttocks or

the back of the neck. There is marked fibroblastic proliferation, which, with intercellular formation of fibrin, causes the characteristic induration. The tension thus becomes high and is responsible for the pain. There may be very little liquefaction of the necrosed tissue, so that the center of the boil is composed of a solid "core" instead of pus. In a *carbuncle* the infection spreads to the subcutaneous tissue where it causes a more diffuse lesion which discharges on the surface by a series of openings, and from which toxic absorption is more liable to occur. The pus serum is absorbed into the lymphatics, the pus becomes inspissated, and the dead tissue is converted into a mass of fatty debris in which lime salts may be deposited. This fatty change with calcification is seen much more commonly in tuberculous lesions than in acute inflammation.



FIG. 48.—Non-healing ulcer. The epithelium on the left shows no sign of growing over the inflamed floor of the ulcer.  $\times 125$ .

So far we have only considered suppuration limited to a circumscribed area. The suppuration may spread through the tissues, a condition known as *cellulitis*. Streptococci are more likely to cause a spreading inflammation, staphylococci a limited one. This difference depends in part on the intensity of the local inflammatory reaction; this is much more severe in staphylococcal than in streptococcal infections. Menkin claims that this is on account of blocking of the lymph channels by fibrin. Staphylococci produce a clotting principle or staphylocoagulase which favors fibrin formation, whereas streptococci produce a fibrinolytic principle which breaks down and prevents the formation of fibrin. For these reasons the constitutional reaction (due to widespread bacterial invasion) may be in inverse proportion to the intensity of the local reaction.

**Varieties of Inflammation.**—A multitude of descriptive names have been applied to the various forms of inflammation. The meaning of most of these is self-evident, so that they need only be mentioned. An understanding of the principles which underlie the variations is far more important than any string of names. *Serous* inflammation is characterized by

an exudate composed chiefly of serum. Pleurisy with effusion is an example. In *fibrinous* inflammation the chief element is fibrin. It is seen in dry pleurisy, in diphtheria, and in pneumonia. *Purulent* inflammation is suppuration. *Catarrhal* inflammation is a mild inflammation of a mucous membrane; the mucous cells pour out mucus with which are mingled desquamated epithelial cells and a certain number of leucocytes, but the process stops short of suppuration. A cold in the head is an example. *Membranous* or *diphtheritic* inflammation is a condition where the cells of a mucous surface are killed, an exudate is laid down on the surface, and the whole necrotic layer is bound by fibrin to the underlying tissue to form a "false membrane."

**ALLERGIC INFLAMMATION.**—When an animal or person is sensitized to bacteria by previous inoculation (*i. e.*, is in a state of allergy), a subsequent injection of the same organisms will cause a violent local reaction with inflammatory changes which are much more extreme than in the normal animal. This condition may be called allergic inflammation. Its two main features are: (1) the large amount of exudate and the tendency to necrosis and destruction of tissue, owing to the union of antigen and antibody within the cells; (2) the increased phagocytic power of the leucocytes and macrophages, as a result of which the infection is more readily overcome. In the chapter on Infection and Resistance we shall have occasion to observe that only the first of these features is a manifestation of allergy, the second being dependent on the acquired immunity which accompanies the allergic state. If the condition is of benefit to the animal it is on account of the second, not the first, of these features.

**INFLUENCE OF CORTISONE ON THE CELLS OF INFLAMMATION.**—Far-reaching effects upon the dynamics of inflammation have been ascribed to secretions of the adrenal cortex (Dougherty and Schneebeli, Rebuck and his associates). These effects are produced both by cortisone and ACTH, and have been observed in the experimental animal and in man. The cortisone may be used topically as well as parenterally. In the human subject the technic of skin windows has been used effectively (Rebuck *et al.*). This consists of scraping the epidermis over a small area, the application of an antigen (egg white, diphtheria toxoid, old tuberculin, etc.) to the denuded surface, and overlaying the lesion with a small cover-slip. The exudative cells migrate to the undersurface of the cover-slip within thirty minutes. The cover-slip is removed, stained, and replaced by others as often as is desired.

The most striking changes concern the lymphocytes. There is marked depletion of these cells at the period when they should appear (eight to twelve hours), and later of the macrophages into which the lymphocytes develop. These results seem to be brought about by injury to the lymphocytes in the lymphopoietic tissues, depletion of lymphocytes in the circulating blood and inhibition of lymphocytic migration. Phagocytic activity is diminished to a marked degree. This involves the polymorphonuclears directly and the macrophages indirectly on account of depletion of the lymphocytes from which they develop. Other well-known results of the administration of cortisone and ACTH are inhibition of the growth of granulation tissue and depletion of eosinophils in those cases in which



these cells form part of the inflammatory exudate. The antispreading effect of cortisone due to inhibition of the spreading factor, hyaluronidase, may also have to be considered.

The basic disturbances are damage to the organ sources of lymphocytes, inhibition of phagocytosis, decrease of the margination and migration of leucocytes in the vessels, possible interference with transport of the white blood cells, and local inhibition of the defense mechanism.

Most of the changes described above are likely to be deleterious in effect, especially if the exciting agent is virulent and capable of reproduction. Both the morbidity and mortality are increased in many experimental infections induced by bacteria (pneumococci, staphylococci, streptococci, tubercle bacilli) and by viruses (poliomyelitis, vaccinia, influenza). The incidence of spontaneous infections is increased and there is recrudescence of chronic and latent infections. If, on the other hand, the antigen is not virulent nor capable of reproduction, the toning down or inhibition of the normal inflammatory response might protect such delicate structures as arterioles, glomeruli and the eye. The remarkable effect of cortisone on the lesions of chronic arthritis are well known and a similar beneficial result may be obtained with the vascular lesions of periarteritis nodosa (Baggenstoss).

**Chronic Inflammation.**—When an irritant of low-grade intensity acts upon the tissues the result is said to be chronic inflammation, because it does not run the rapid acute course characteristic of acute inflammation. The tissue reaction is quite different from that of the acute form. It is often said to be productive in character, but the cells which collect in response to the irritation either come from the blood stream (lymphocytes, etc.), or are derived from those wandering tissue cells which go by the alternative names of histiocytes, mononuclears and macrophages. The only cells which proliferate are the fibroblasts.

The *infectious granulomas* form a special group. The most important member of the group is tuberculosis, but it also includes syphilis, leprosy, and the mycoses which are caused by fungus infection. In its original sense a granuloma was a mass made up of granulation tissue, but it has come to signify an infective condition in which histiocytes are the principal cells, although lymphocytes, and plasma cells often play an important part. The histiocytes may become swollen, often containing lipoid material in tuberculosis; such swollen cells are referred to as *epithelioid cells*. These may fuse together to form the *giant cells* which are characteristic not only of all the chronic granulomata, but also of the inflammatory reaction produced by a foreign body. The accumulation of cells may be so great that the lesion may form a tumor-like swelling; this is the reason for the misleading term productive inflammation.

In an organ such as the liver or kidney an intense irritant producing acute inflammation will destroy both the highly specialized parenchymatous cells and the more lowly developed connective tissue. An irritant of low intensity may kill the special cells, but only stimulate the fibrous tissue to proliferate (fibrosis), just as a degree of cold which will kill a race horse may merely stimulate a cart horse. John McCrae, the poet pathologist

who wrote "In Flanders Fields," compares the parenchymatous cell to the professional man in a community, specially trained, not prone to be physically hard, nor overgiven to reproduction. The supporting cell is its laboring-class brother, physically strong, not readily injured, but ready in reproduction.

A chronic inflammatory lesion is cellular at first, but becomes more and more fibrous as the irritation subsides and collagen is laid down. It follows the usual course of healing. But it is obvious from the nature of the process that the resulting fibrosis is likely to be much more marked than in acute inflammation. Newly-formed fibrous tissue invariably contracts as it becomes older, so that the affected organ will be shrunken as well as hard. Examples of these changes are healed tuberculosis of the lung and cirrhosis of the liver.

One word regarding nomenclature. A healed inflammatory lesion is not an example of chronic inflammation. It is not an "itis," so that when the surgeon finds a firm and shrunken appendix it does not follow that the patient is suffering from chronic appendicitis. The appendix may be chronically inflamed, or it may be merely a fibrosed appendix; microscopic examination is necessary to settle the question. This subject is brought up because of a loose habit, all too common, of speaking of chronic appendicitis, chronic myocarditis, or chronic pleurisy when the speaker really means a fibrosed appendix, myocardium, or pleura.

## ADDITIONAL READING

- Bacterial Invasion.** GOODPASTURE AND ANDERSON: *Am. J. Path.*, 1937, 13, 149.  
**Cells of Inflammatory Exudate.** BEATTIE: *J. Path. and Bact.*, 1902, 8, 129. FOOT: *Anat. Rec.*, 1925, 30, 15. FRIED: *Arch. Path.*, 1934, 17, 76.  
**Chemotaxis.** McCUTCHEON: *Arch. Path.*, 1942, 34, 167.  
**Cortisone and Inflammation.** BAGGENSTOSS *et al.*: *Am. J. Path.*, 1951, 27, 537. DOUGHERTY AND SCHNEEBELI: *Proc. Soc. Exper. Biol. and Med.*, 1950, 75, 854. REBUCK *et al.*: *Gastroenterology*, 1951, 19, 644. *Am. J. Path.*, 1953 (*in press*).  
**Dynamics of Inflammation.** MOON AND TERSHAKOVEC: *Arch. Path.*, 1951, 52, 369.  
**Emigration of Leucocytes.** CLARK AND CLARK: *Am. J. Anat.*, 1935, 57, 385.  
**General References.** ADAMI: *Inflammation*, London, 1909. COHNHEIM: *Lectures on General Pathology* (English translation), London, 1889. KLEMENSIEWICZ: *Die Entzündung*, Jena, 1908. MARCHAND: *Lehre von der Entzündung* (in Krehl and Marchand: *Handbuch der allg. Path.*, 4, 78, Leipzig, 1924). METCHNIKOFF: *The Comparative Pathology of Inflammation* (English translation), London, 1893. RICH: *Arch. Path.*, 1936, 22, 228. WELLS: *Chemical Pathology*, Philadelphia, 1925.  
**Giant Cells.** HAYTHORN: *Arch. Path.*, 1929, 7, 651.  
**Histamine.** LEWIS: *The Blood Vessels of the Human Skin and Their Responses*, London, 1927; Heart, 1926, 13, 1.  
**Inflammation and Immunity.** OPIE: *J. Immunol.*, 1929, 17, 329. RICH AND McKEE: *Bull. Johns Hopkins Hosp.*, 1934, 54, 277.  
**Inflammation and Infection.** KETTLE: *Lancet*, 1927, 1, 1169, 1225. RICH: *Arch. Path.*, 1936, 22, 223.  
**Localization of Inflammation.** MENKIN: *Am. J. Med. Sci.*, 1935, 190, 583.  
**Lymphocytes.** BERMAN: *Arch. Path.*, 1942, 33, 295. KOLOUCH: *Am. J. Path.*, 1939, 15, 413. McMASTER AND HUDACK: *J. Exper. Med.*, 1935, 61, 783.  
**Lymph Flow.** FIELD, DRINKER AND WHITE: *J. Exper. Med.*, 1932, 56, 363.

**Lymphatics in Inflammation.** PULLINGER AND FLOREY: J. Path. and Bact., 1937, **45**, 157.

**Macrophages.** EBERT AND FLOREY: Brit. J. Exper. Path., 1939, **20**, 342. MACCALLUM: Textbook of Pathology, Philadelphia, 1940.

**Mast Cells.** JORPES: Heparin: its Chemistry, Physiology and Application in Medicine, London, 1939.

**Permeability of Capillaries.** MENKIN: J. Exper. Med., 1936, **64**, 485.

**Phagocytosis.** CARREL AND EBELING: J. Exper. Med., 1926, **44**, 285. EVANS: Arch., Int. Med., 1916, **18**, 692. FRIED: Arch. Path., 1938, **26**, 700. JACOBSTHAL: Virchows' Arch. f. path. Anat., 1921, **234**, 12. MUDD AND MUDD: J. Gen. Physiol., 1933, **16**, 625.

**Stellate Inclusions In Giant Cells.** CUNNINGHAM: Am. J. Path., 1951 **27**, 761.

## Chapter

# 5

## REPAIR

THE repair of injured tissue is as fundamental a process as inflammation. It is seen throughout the animal and vegetable kingdom. The lower in the scale the animal, the more complete is the regeneration. When the head of the earthworm is severed, a new one is formed, and this process can be repeated many times. The process of repair is so commonplace that we seldom pause to enquire what induces cells which have remained dormant for years suddenly to take on active growth. When looked at closely this is seen to be a remarkable phenomenon. Incise the most quiescent of fibrous tissue, and in twenty-four hours the connective-tissue cells have developed from mere nuclei into actively dividing fibroblasts. What is the cause of this sudden transformation? What is the *vis medicatrix naturae*, the healing power of Nature?

It seems likely that the cells proliferate because they are stimulated. The stimulus is almost certainly chemical in nature. This chemical substance appears to be liberated by the degenerating cells. Carrel has shown that if in an aseptic wound all débris and blood clots are removed and the wound is completely protected from outside irritation no healing will occur. Even at the end of three weeks no change has occurred. But when the wound was covered with a slightly irritating dressing such as dry gauze or a weak turpentine dressing or when a few staphylococci were introduced, cicatrization commenced in less than two days.

The power of true repair, that is to say of replacement of destroyed tissue by the same type of tissue, varies with different organs. Some cells have developed to a stage at which it is impossible for them to proliferate, *e. g.*, nerve cells. When such cells are destroyed by injury or infection, as in infantile paralysis, it is impossible for them to be replaced by neighboring cells; "the moving finger writes, and, having writ, moves on." Liver cells have remarkable power of regeneration. So has surface epithelium. Connective tissue is the best example of perfect regeneration.

It is difficult to draw a hard and fast line between repair and inflammation. Both represent the reaction of the tissues to an irritant. Repair usually follows inflammation, and is usually preceded by it, but not always so. An irritant of some intensity produces inflammation and death of the tissues. At a distance the action is weakened, and the irritant becomes a stimulant, so that the tissue response now is proliferation. In this way reparative processes may go on at the same time as inflammation.

The most interesting modern observations on repair are those of Clark and his associates. By inserting a double-walled transparent chamber constructed of celluloid in a rabbit's ear they have been able to watch

under the microscope the injured tissues recovering from the blow and setting themselves to reconstruct the part. They have even taken moving-picture microphotographs of the process. By this means new vessels can be seen differentiating and beginning to contract and dilate. Using intravital injections of methylene blue they could demonstrate the development of non-medullated nerve fibers going to the arteries; only when the vessels were supplied with nerves were they capable of contraction. The ingrowth of capillaries is followed by a remodelling of the indifferent plexus of vessels into an adult pattern, and a change into definite arteries and veins. The same is true of lymphatics, which also grow by sprouting, and appear later than the blood vessels. Even the different stages of mitosis were seen and photographed. After injury associated with edema definite holes could be seen in the lymphatics which remained open for several days, allowing free passage of fluid and red blood cells into the injured lymphatics. This passage was not observed when the ear was splinted, thus demonstrating the importance of immobilization in the treatment of localized injuries and infections in order to prevent the entrance of bacteria into the lymphatics.

One of the most important elements concerned with repair is connective tissue. This is particularly true of repair of wounds. The formation of collagen satisfactory in quantity and quality is dependent on an adequate supply of vitamin C. In the early stage of wound healing acid mucopolysaccharides (hyaluronic acid) are produced. In the absence of vitamin C this substance is lacking but it reappears on injection of the vitamin. (Penney and Balfour). Scurvy which is due to lack of vitamin C, is characterized by atrophy of connective-tissue fibers, and under scorbutic conditions fibroblasts produce little collagen, and what is produced is of poor quality. It is evident, therefore, that an adequate supply of vitamin C is necessary for good healing. It has been shown clinically that when the vitamin supply is insufficient the healing of wounds is delayed and they tend to break open again (Crandon, Lund and Dill).

*Cortisone* interferes with the process of repair in the experimental animal, as well as inhibiting the vascular and exudative changes of inflammation. There is an almost complete lack of fibroblastic and vascular proliferation, migration of histiocytes, foreign body giant cell formation, and development of adhesions. Some workers find that these effects are only observed after a lag of a day or two (Lattes *et al.*). It seems probable that the cortisone interferes with chemical changes in the mucopolysaccharides of the ground substance of connective tissue, changes which are initiated by release of agents as the result of injury and are indicated by metachromasia of the ground substance. Other steroid hormones also influence repair. Thus desoxycorticosterone stimulates the proliferation of fibroblasts and encourages the formation of collagen in the wall of a chemically-produced abscess, whilst testosterone and estradiol have the opposite effect (Taubenhaus and Amronin). The sex hormones may act by inhibiting the anterior pituitary.

The experimental observations outlined above may or may not be of importance in human pathology. The dose of cortisone used on the animals

is very much greater than the human dose. Surgical evidence in man suggests that a wound in a person on cortisone therapy should heal well. On the other hand there seems to be a tendency for perforation of a gastric ulcer, and for interference with reparative fibrosis in pulmonary tuberculosis.

Repair is a wide process. It is seen in the healing of wounds. Exactly the same changes are observed in organization of an inflammatory exudate or a blood clot. The regeneration or replacement of any destroyed or degenerated tissue is another example of the same process. All of these must now be considered in greater detail.

**Repair in a Wound.**—The process of healing is fundamentally the same in all wounds, but there are marked quantitative differences, depending on the amount of tissue destruction and to a certain extent on the presence of sepsis. It is convenient to consider two very different types of wound.

**HEALING OF A CLEAN INCISED WOUND.**—This form of repair is still known by the old clinical name of "healing by first intention." A much better term is "primary union," the cut surfaces being brought together by stitches, so that the process is direct, with no intermediary substance playing a part. There is no appreciable loss of substance, bleeding is at a minimum, infection is absent, and if the edges are brought into apposition there is hardly any exudate between the surfaces. The knife acts as an irritant, so that the edges will show slight inflammatory changes in the shape of vascular dilatation and exudation, and a small quantity of plasma, fibrin, and leucocytes will be present in the thin gap. Although the wound is strictly *aseptic*, it is not bacteriologically *sterile*, and *Staphylococcus albus* may be present in small numbers. We have already seen that this tends to favor healing rather than to retard it.

The edges of the wound very soon show that they are under the influence of a stimulant. Two types of cell divide actively, the connective-tissue cell and the vascular endothelial cell. In both, mitotic figures may be seen, particularly in the former. (Fig. 49.) The connective-tissue cell or fibrocyte of adult fibrous tissue is little more than a narrow nucleus surrounded by a thin layer of cytoplasm and wedged between dense bundles of collagen fibers, but it rapidly changes into a plump fusiform cell with a

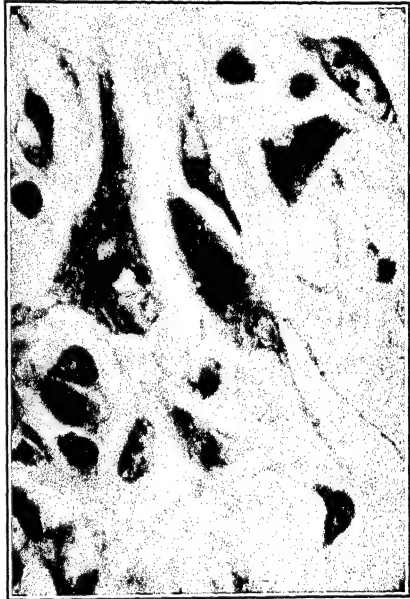


FIG. 49.—Proliferating fibroblasts, one of which shows a mitotic figure.  $\times 800$ .

large nucleus and well-developed cytoplasm which may end in branching processes. The sudden change from complete quiescence to extreme activity denotes the action of a powerful stimulant.

The mode of growth of the fibroblasts may best be studied by the method of tissue culture. The colonies of fibroblasts in culture medium tend to grow toward one another, as if the cells of one attracted the cells of the other. The coagulated plasma between the edges of the wound plays the part of a medium into which the fibroblasts grow and establish connection with those on the other side. Carrel has studied the motion of the fibroblasts in tissue culture by means of the cinematograph. The cells when photographed and projected on a screen can be seen to move through the

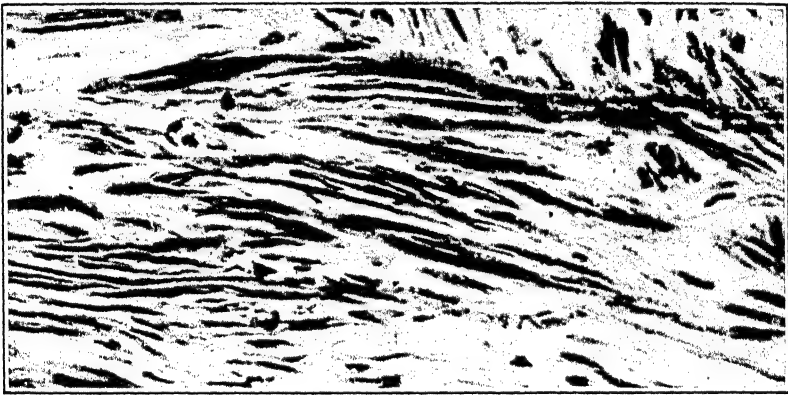


FIG. 50.—Fibroblasts separated by scanty collagen.  $\times 275$ .

medium in straight lines. The anterior process streams through the medium; then the nucleus and cytoplasmic body move forward. From such a picture it is easy to understand how the fibroblasts will rapidly unite the opposing surfaces. In culture the fibroblasts are seen always to keep in touch with their fellows, thus differing from the macrophages which wander about and live as independent units.

The fibroblasts proceed to lay down collagen fibers. (Fig. 50.) The fibril formation takes place at the expense of the cell bodies until finally these are represented by a thin, drawn-out nucleus surrounded by a delicate layer of cytoplasm. The collagen fibers form wavy bundles of *scar tissue*. (Fig. 51.) By this process of fibroblastic proliferation and immigration together with the formation of fibrils of increasing density the two surfaces of the wound are firmly sewn together. When the fibers are fully formed they shorten, and this contraction continues for some months, so that the scar which was at first raised becomes puckered.

Synchronously with the fibroblastic proliferation there occurs a proliferation of vascular endothelium. Protoplasmic buds are formed from the preëxisting endothelium, and these establish connections with other buds until a branching network is formed. The buds become hollowed out, and a lumen is established which is continuous with the lumen of the

parent capillaries. Marked vascularity is a fundamental characteristic of tissue undergoing repair, for an abundant blood supply is needed for the rapidly growing cells. The scar which first forms is therefore red. When repair is complete the stimulus to proliferate is withdrawn, a high degree of vascularity becomes unnecessary, and the vessels gradually disappear, so that the scar is avascular and white.

Pullinger and Florey using the transparent chamber in the mouse's ear introduced by Smith, found by direct observation that lymphatic capillaries proliferate in the same manner as the blood vessels. A remarkably rich capillary network is established in ten to twelve days which can be demonstrated by injection. These new lymphatics no doubt play an important part in removal of the exudate. As healing proceeds they retrogress and finally disappear.

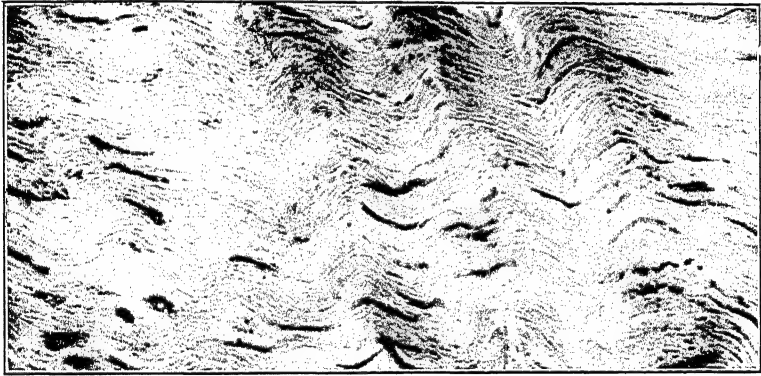


FIG. 51.—Scar tissue. Bundles of collagen fibers, between which are flattened fibroblasts.  $\times 400$ .

The epithelium from the sides grows over the narrow gap. It might be thought that the new epithelial cells were produced by mitosis. This is not the case. The defect is made good by the migration or sliding of cells from the edge of the wound. Mitoses are found regularly at some distance from the edge. At first the epithelial layer is thin and bluish in color, a mere layer or two of cells, but soon it becomes thick and white. The specialized structures of the skin such as hair follicles and sweat glands are not replaced. The scar is pale, without hair and without sweat.

The time at which the various steps occur differs with differing conditions, but on an average it may be said that fibroblastic and endothelial proliferation occurs by the end of twelve hours, the epithelium has covered the surface and the edges are firmly sewn together by the fourth day, and at the end of three weeks there is fully formed non-vascular scar tissue. The active process of primary union takes about five days, and nothing but a thin line of connective tissue remains to indicate the site of the wound. If the wound is irritated there will be a more abundant exudate, more fibroblasts are formed, and the scar will be thicker. If the wound is badly infected suppuration will occur, and there will be no primary union.



**HEALING OF AN OPEN WOUND.**—When there is loss of substance the fibroblasts are unable to sew the surfaces together, and the gap is filled from below by a mass of young vessels and cells called granulation tissue. This is healing by granulation as opposed to healing by primary union. In time the granulation tissue becomes organized, *i. e.*, converted into fibrous tissue, a process known as cicatrization. Epithelium covers the surface, and the gap is closed.



FIG. 52.—Granulation tissue. Young vascular connective tissue consisting of new capillaries and fibroblasts, together with many inflammatory cells.  $\times 350$ .

The gap is first filled with a mixture of coagulated blood, fibrin, and inflammatory exudate, and upon this scaffold the fibroblasts and vascular endothelium build the granulation tissue. (Fig. 52.) The process commences at the base and works to the surface, so that the youngest tissue is always at the surface. It is on the surface that the granulations are formed which give the name to the whole mass of young vascular connective tissue. When the surface of a clean open wound is examined at the end of the second day it is seen to be covered with tiny red granules, so that it has the appearance of a pile of rough velvet. This red, finely granular surface is an indication of normal and healthy healing. Such a surface is highly vascular and bleeds very readily. If a dry gauze dressing sticks to the surface and is then torn off, the capillary loops are ruptured, and the process of healing is materially interfered with.

In addition to the fixed cells of the part (fibroblasts and vascular endothelium), wandering cells also form an important element of granulation tissue.

In the early stages these are mainly polymorphonuclear leucocytes, which migrate from the new capillaries in response to the irritation and appear on the surface in large numbers in the scanty exudate which our forefathers used to call "laudable pus." They doubtless serve to keep the surface free from infection. In the later stages and in the deeper layers the wandering cells are mainly macrophages and lymphocytes. The macrophages provide an even greater protection than the polymorphonuclears, for it can be shown experimentally that if an aseptic inflammation be pro-

duced and infection be added later, the substances which call forth macrophages in the aseptic inflammation give much better protection than those which call forth polymorphonuclears. Not until the leucocytes have overcome the infection does the epithelium begin to cover the surface, and true healing can be said to have commenced.

On account of its cellularity a granulating surface has a remarkable power of resisting bacterial infection. It presents so powerful a barrier that septicemia (blood invasion) cannot occur once an intact wall of granulation tissue has been formed. Billroth demonstrated this experimentally as long ago as 1865 by applying septic dressings soaked in putrid pus to the surface of a granulating wound. No infection resulted; but if the dressings were stitched in position, the stitch holes in the healthy skin at once became infected. Burrows found that when virulent streptococci were injected into the freshly epilated skin of a rabbit severe inflammation resulted, but that if there was an interval of five days between the two procedures, no inflammation developed. Crystalline substances in solution are rapidly absorbed, probably on account of the great vascularity of the surface, so that death may follow the application of a poisonous substance like corrosive sublimate, and it is said that opium will occasion sleep nearly as quickly as when given by mouth.

The granulation tissue grows in maturity from below upward. In the superficial layers the fibroblasts run at right angles to the surface and therefore parallel to the vessels, but in the deeper parts of the wound where the process is older they are arranged parallel with the surface, and eventually all the fibroblasts and the fibers which they produce run in this direction. The direction depends largely on the pull which is exerted on them. If this be altered experimentally, the direction of the fibroblasts will be correspondingly changed.

When the wound is aseptic the epithelium will grow in from the edge in two or three days, first as a delicate blue pellicle, gradually becoming thick and opaque. To say that the wound is aseptic does not mean of course that it is bacteriologically sterile. If there is sepsis and active inflammation the surface is bathed in pus, and the epithelium shows no sign of activity. In a chronic ulcer, where for some reason healing is long delayed, the epithelium sends long processes down into the deeper tissues. These may appear to be detached from the surface in a microscopic section, and may be very suggestive of carcinoma. In some cases a malignant growth may actually commence in such a chronic ulcer.

When the surface is covered by epithelium the process of devascularization begins. The new vessels being no longer needed gradually disappear, and the scar which is first red and angry-looking becomes white and bloodless.

Healing of a wound may be interfered with by a number of factors, one of the most important of which is protein deficiency. It would appear that a food factor of special importance is the amino acid methionine (Perez-Tamayo and Ihnen). When animals with experimental wounds are kept on a protein-free diet for a short time, only a narrow zone of reaction develops, the new capillaries and fibroblasts are few in number, and there

is a marked delay in the formation of fibers. The result is a weak scar with decreased tensile strength. When, however, methionine is added to the diet normal connective tissue of normal tensile strength is formed. As regards wound healing protein deficiency seems to mean thiamine deficiency. This amino acid increases the rate of utilization of the protein available, and its sulphur radicle may also be used for the formation of chondroitin sulphate which imparts firmness to the ground substance.

**Healing of an Abscess.**—All repair is fundamentally the same, whether in an open wound or in an abscess in the center of the kidney. If the infection is destroyed, attempts at repair begin. These are much more successful if the pus can discharge on to a surface, as into the pelvis of the kidney. If the cavity is small it becomes filled up first with granulation tissue, then with scar tissue. If the cavity is large it cannot be filled in, but a fibrous wall is built around it. Healing after appendicitis takes the same course, first granulation tissue, then scar tissue.

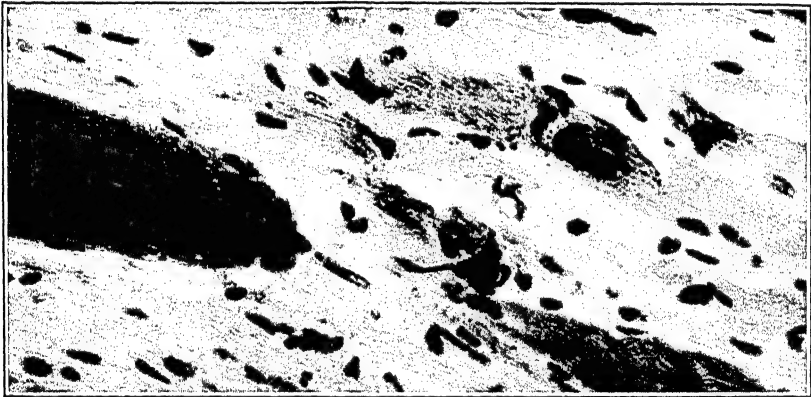


FIG. 53.—Regeneration of muscle showing syncytial masses of sarcolemma.  $\times 300$ .

**Organization of an Exudate on a Serous Membrane.**—When a serous membrane such as the peritoneum is inflamed the endothelial covering is destroyed, and an exudate is formed on the surface consisting mainly of fibrin. This is invaded by fibroblasts and new capillaries, so that the exudate is replaced by granulation tissue, which in turn is fibrosed. The surface endothelium may again cover the fibrous patch, restoring the integrity of the membrane. Or two fibrinous surfaces, *e. g.*, two inflamed loops of bowel, may coalesce and become adherent. The fibrinous adhesions become fibrous, and although the sides of the adhesions are clothed with endothelium the integrity of the surface cannot be restored, and the adhesions are permanent. The fibrous bands contract, and may cause kinking and obstruction of the bowel.

**Organization of a Thrombus.**—A blood clot or thrombus in a vessel undergoes the same changes as an inflammatory exudate. It is invaded from the side of the vessel by fibroblasts and endothelial buds. New capillaries are formed, and a vascular connective tissue gradually takes the

place of the clot. As cicatrization occurs the fibrous mass may shrink from the vessel wall, so that a space is formed which becomes lined by the endothelium of the vessel. In this way a certain flow of blood may be reestablished through the vessel. Occasionally new channels are opened through the clot; these become lined with endothelium, and the clot is said to be canalized.

A brief summary of the healing process in different tissues is all that need be given here. Greater detail will be found in the chapters devoted to the individual organs.

*Epithelium* as it occurs in the skin is repaired rapidly and completely. The more specialized epithelial skin structures such as hair follicles are not replaced. *Connective tissue* is completely replaced, as fibroblasts are the cells of connective tissue. *Elastic tissue* is replaced very slowly, but

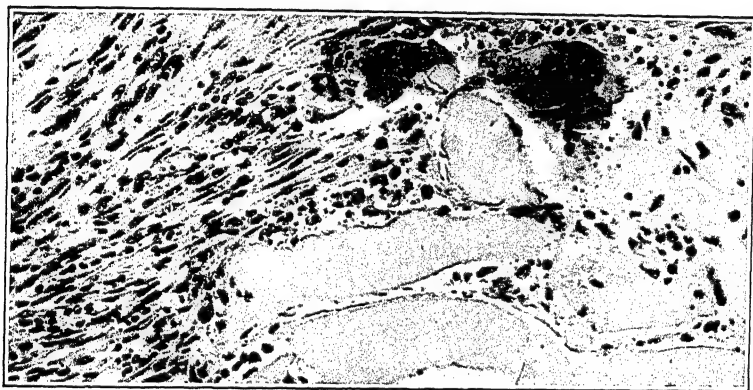


FIG. 54.—Necrotic muscle fibers being removed by giant cells and replaced by fibrous tissue.  $\times 180$ .

fairly completely. *Fat* destroyed in a wound is usually not reformed, but if the fat cells are only partially destroyed new cells smaller in size and containing fine droplets may be formed within them. *Cartilage* is so avascular that healing is very slow and imperfect. If the damage is at all extensive, the replacement is by scar tissue. New cartilage can be formed from the cells of the perichondrium, and small gaps may be filled in this way. Healing in *muscle* depends on the kind of muscle. Plain muscle and heart muscle fibers do not regenerate; union of the divided parts is by scar tissue. Striated muscle has greater reparative power. The extent of regeneration depends on the type of injury. In an incised wound with no loss of substance the nuclei of the sarcolemma proliferate and form multinucleated syncytial masses (Fig. 53) while the sarcous substance puts out bands which bridge the gap and eventually become striated. On the other hand when the muscle fibers have been destroyed the débris is removed by mononuclear phagocytes, which may form giant cells, and the gap is closed by fibrous tissue. (Fig. 54.) *Tendon* is very avascular so that healing is very slow, but it is remarkably complete, though it may take as long as

two months. If the gap is small it is filled completely by tendon cells; if large, scar tissue has to be used. Sepsis is fatal to healing, because necrosis occurs so readily in the non-vascular tendon. Injury of a *serous membrane* is repaired by fibrous tissue which becomes covered by the endothelium of the membrane. A fibrinous exudate is formed on the surface at the site of injury, and the two surfaces tend to be united by adhesions which are at first fibrinous but soon become converted into fibrous tissue. A *mucous membrane* is repaired quickly and well. The surface epithelium is completely replaced, and simple tubular glands can be reformed from this epithelium, but complete restoration of such glands as those of the stomach only occurs when portions of the glands have escaped destruction. Wounds of the *liver* are repaired by scar tissue. The liver cells have great power of regeneration, and this is seen in the necroses of the liver such as acute yellow atrophy and cirrhosis where the lesion is primarily one of the epithelial cells rather than in wounds and abscesses. In the *kidney* there is no regeneration of glomeruli or tubules already destroyed, so that repair is confined to the formation of scar tissue. The *central nervous system* has no power of true regeneration. When a neurone is killed it is not replaced. A wound of the brain is filled by neuroglia which proliferates readily, and to a small extent by the connective tissue which accompanies the blood vessels. The *peripheral nerves*, on the other hand, have remarkable powers of regeneration, a process which will be considered in detail in the chapter on The Nervous System.

*Response to Injury in Different Tissues.*—When some organs, such as liver and pancreas, are injured by brief freezing the necrotic tissue is removed quickly and completely and replaced by reparative tissue. With other tissues, such as testis and kidney, the process is very much slower (Cameron and Mehrotra). In the liver polymorphonuclear infiltration is marked in twelve hours, a wide layer of granulation tissue is formed in two days, and there is complete replacement by scar in five days. In the testis, on the other hand, although necrosis is complete in twelve hours, polymorphonuclears are few in number, there is little change during the next few days, and only a small amount of granulation tissue is formed by the end of five days. This variation in tissue response may be referred either to the injured cells or to the cell environment. If the necrotic piece of liver is inserted in the omentum or testis, replacement by fibrous tissue is not complete until the end of 28 days, and when the piece of frozen testis is inserted in the liver the time of replacement is the same as in the testis itself. These experiments indicate that a change in environment prolongs the inflammatory and reparative reaction in the case of the one tissue but not of the other, so that the cells throughout the body should be thought of in terms of their immediate environment as well as their own characteristics. Cameron and Mehrotra suggest that for this dual and reciprocal relationship the term “field” is suitable. The result of cellular injury may vary with the environment, which is itself affected by the products of cell injury. This also suggests the question of the reaction to various kinds of injury in diseased tissues as opposed to the response in normal tissues, quite a different state of affairs. The relation of the cells

of an epithelial tumor to the surrounding stroma is also another matter, yet related to the concept of field of influence.

A century and a half ago Virchow introduced us to the concept of cellular pathology, which marked the birth of modern pathology. Today we are beginning to realize that the ground substance with its mucopolysaccharides is the foster parent of the cellular parenchyma, determining the state of health or disease of the cells to a degree that no parent can ever attain.

## ADDITIONAL READING

**Absorption from Granulating Surface.** WHITE: *Lancet*, 1931, **1**, 1293.

**Cortisone and Repair.** LATTES, *et al.*: *Am. J. Path.*, 1953, **29**, 1. TAUBENHAUS and AMRONIN: *Endocrinology*, 1949, **44**, 359.

**General References.** BURROWS: *Some Factors in the Localization of Disease in the Body*, London, 1932. CLARK, *et al.*: *Am. J. Anat.*, 1932, **52**, 49, 273; 1934, **55**, 47. MARCHAND: *Der Prozess der Wundheilung*, Stuttgart, 1901.

**Growth Stimuli.** CARREL: *J. A. M. A.*, 1924, **82**, 255. HAMMETT: *Protoplasma*, 1929, **7**, 297. HUEPER: *Arch. Path.*, 1934, **17**, 218.

**Healing.** CARREL AND EBELING: *J. Exper. Med.*, 1926, **44**, 285. PULLINGER AND FLOREY: *J. Path. and Bact.*, 1937, **45**, 157. PEREZ-TAMAYO AND IHEN: *Am. J. Path.*, 1953, **29**, 233.

**Healing in Relation to Vitamin C.** CRANDON, *et al.*: *New England J. Med.*, 1940, **223**, 353.

**Response to Injury in Different Tissues.** CAMERON AND MEHROTRA: *J. Path. and Bact.*, 1953, **65**, 1. CAMERON: *Pathology of the Cell*, Edinburgh and London, 1952.

## Chapter

## 6

# INFECTION AND RESISTANCE

INFECTION signifies invasion of the tissues by pathogenic microorganisms or animal parasites, and the results both local and general which follow upon that invasion. These results vary enormously. They may remain strictly local, as in a skin abscess or boil due to staphylococci, or they may be general, as in blood invasion by streptococci. There may be an acute inflammation produced by the pyogenic cocci, or a slow proliferative change as in tuberculosis or syphilis, or the microorganisms may remain at the site of invasion but exert a toxic action on a distinct organ such as the spinal cord (as in tetanus). The same infection may produce very different effects in different persons. These variations depend on two great factors, the virulence of the microorganisms and the resistance of the patient. The subject may conveniently be divided into two sections, infection and immunity.

**Localization of Infection.**—Once infection has occurred, its localization depends on a number of factors. When the organisms have entered the body, as through a wound in the skin, they may be held more or less *in situ* or they may drift through the tissues with amazing rapidity. It is evident that the consequences to the patient will be entirely different in the two cases. Local fixation is seen in a striking form in an animal which has been actively immunized, and of course even more so in an animal which is naturally immune. When tubercle bacilli are injected into the skin of a normal animal they spread from the site of inoculation in the course of an hour, so that excision of the area after that time fails to save the animal, and when placed in the peritoneal cavity they are found in the regional lymph nodes in the course of five minutes. If the animal has previously been immunized, the bacilli remain, for a time at least, at the site of inoculation.

Menkin is of the opinion that the local fixation is due to the formation of a fibrinous network both in the lymphatics and the tissues, although many lymphatics still remain open so that the lymph flow from the part may be accelerated, as Drinker has demonstrated. The network of fibrin is abundant in staphylococcal infection, scanty or absent in streptococcal infection, thus accounting for the localized character of the former and the spreading character of the latter.

The beautiful experiments of Rich are of particular interest in this connection. Working with the pneumococcus, an organism which rapidly spreads through the tissues of the rabbit and kills it in from twenty-four to thirty-six hours, he compared the local lesions produced by inoculation of normal animals and of animals which had been rendered immune but

not allergic to the pneumococcus. In the normal animal the organisms at once began to drift through the tissues as each one divided into two and the pair separated, while in the immunized animal they rapidly clumped together and remained *in situ*, as if glued to the part. (Fig. 55.) The process is one of agglutination, an increase of stickiness, as a result of which the bacteria adhere to one another and to the tissues with which they come in contact. Large clumps were formed in the course of thirty minutes, but at that time there was no inflammatory exudate, no fibrin formation.

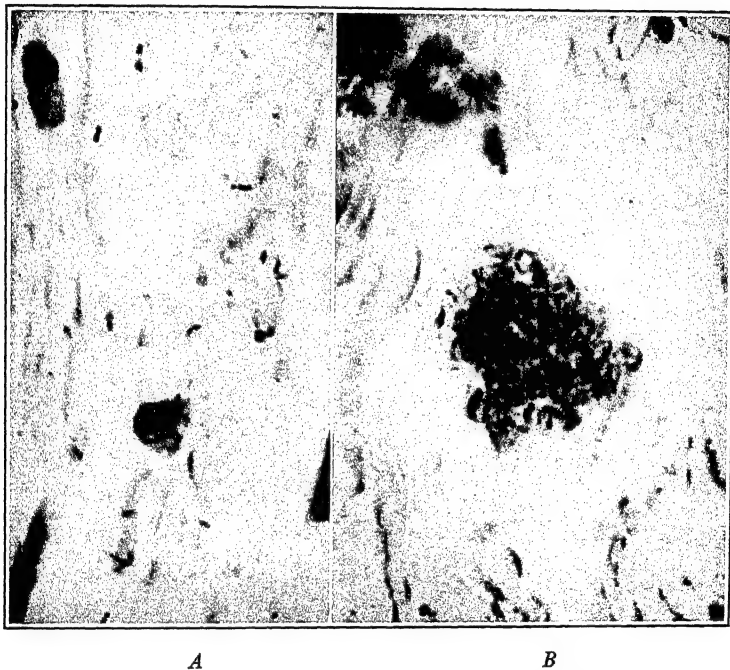


FIG. 55.—*A*, Site of infection in non-immune rabbit four hours after injection of pneumococci; cocci drifting through the tissue; *B*, the same in an immune rabbit four hours after injection; the proliferating cocci are clumped together. (Rich, Bull. Johns Hopkins Hospital.)

So far we have discussed the mechanism by which bacteria which gain entrance to the tissues are held locally and prevented from setting up a general blood infection. Now we may turn to the converse of this question. When organisms are circulating in the blood their localization in the tissues depends largely on the permeability of the capillaries, which in turn is governed by such a factor as trauma, causing the liberation of histamine and resulting local capillary paralysis with increased permeability. When trypan blue is injected intraperitoneally in rats, and the animals are then struck on the head repeatedly, the dye is found to be localized in the brain (Macklin). When the dye is injected intravenously and a hot-water bag is applied to the abdomen, the dye will stain not only the abdominal wall but also the subjacent coils of bowel. As the result of a similar mechan-



ism, bacteria circulating in the blood will tend to become localized at the site of injury. Should hemorrhage have occurred, the bacteria will leave the blood stream still more readily. A common clinical example is the relation of trauma to acute osteomyelitis.

The question of localization of infection does not depend, however, entirely on the tissues and fluids of the body. The bacteria themselves have something to say on the matter of invasiveness. Duran-Reynals has shown that invasive strains of staphylococci and streptococci contain a soluble factor which can be extracted, and which markedly increases tissue permeability and enhances the infections produced by these organisms as well as by other bacteria. This is known as the *Duran-Reynals* or *spreading phenomenon*. Non-invasive strains of the same species of staphylococci and streptococci do not contain this factor. A similar spreading factor is contained in large amounts in the normal testicle. The factor has been shown by Chain and Duthie to be hyaluronidase, an enzyme which acts on hyaluronic acid, the mucopolysaccharide which forms the ground substance of mesenchymal tissue.

**Results of Infection.**—Bacterial invasion usually produces a local lesion at the site of entry, but there may be no indication of a lesion to the naked eye. Tubercle bacilli when placed in the eye may cause enlargement of the cervical lymph nodes with no disturbance in the eye. The same bacilli may pass through the wall of the bowel and infect the mesenteric lymph nodes. An unrecognizable lesion of the finger may give rise to fatal streptococcal blood poisoning. Even in these instances, however, microscopic examination will show some change in the tissue.

The common result of infection is *local inflammation*. This may be acute, as in the case of the pyogenic bacteria, or the reaction may be chronic in type, as in tuberculosis and syphilis. The microorganisms may be killed by the inflammatory leucocytes, so that the infection ceases there and then. Sometimes the infection becomes quiescent but does not die out, and may at any time re-awaken into activity; a chronic abscess of bone or a quiescent tuberculous lesion in the lung is a sleeping volcano of this kind.

Instead of remaining localized and giving rise to an abscess, the infection may *spread*. Streptococcal infections show a marked tendency to extend, and the most virulent strains may spread at an appalling speed. The power of spread is largely dependent on the production of hyaluronidase, the spreading factor enzyme which depolymerizes hyaluronic acid. When this natural barrier is broken down, a spreading cellulitis is the result. An even more rapid spread may occur along the lymphatics, and lymph nodes at a distance may be infected in a few hours. The microorganisms may be arrested and destroyed in the lymph nodes; they may cause suppuration and breaking-down of the nodes, or they may pass through the nodes and enter the blood stream. The infection then becomes a general blood infection.

**SEPTICEMIA AND BACTEREMIA.**—Septicemia is a commonly used term, but it is most difficult to define. When microorganisms circulate in the blood stream the patient has a bacteremia. This does not necessarily mean that he is ill. It is probable that bacteria continually gain access to the blood from the mouth and through the intestinal wall, but the life of these

bacteria is short. When bacteria are injected into the subcutaneous tissue of an animal they can be found within a few minutes in the liver, heart, and lungs, but they soon disappear. It is probable that in all infections a bacteremia occurs at some stage. In typhoid fever the blood is flooded with bacilli at the beginning of the illness and the same is true of lobar pneumonia. To none of these conditions is the term septicemia applied. Septicemia is a clinical rather than a pathological conception. In addition to the presence of a bacteremia, the patient manifests symptoms which are known as septicemia, such as high fever, chills, and petechial hemorrhages in the skin. The prognosis at once becomes much more serious. Microorganisms are present in the blood in large numbers. They are readily demonstrated by blood culture, and when the infection is very heavy they can be seen in

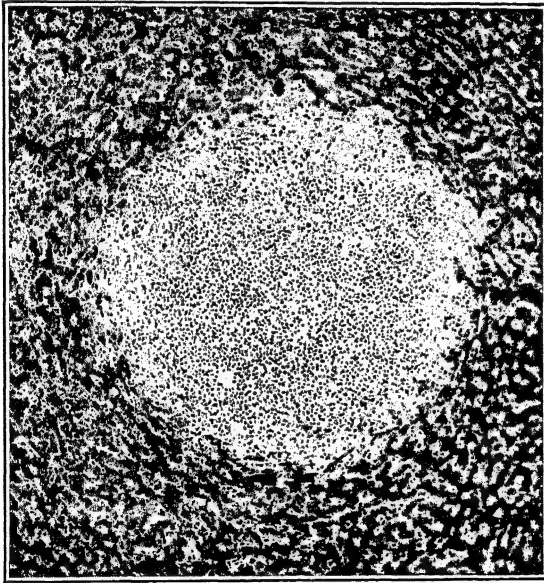


FIG. 56.—Pyemic abscess in liver.  $\times 200$ .

blood smears, as in some cases of streptococcal and meningococcal septicemia. Their great numbers may be due partly to multiplication in the blood, but mainly to a continual pouring of bacteria into the blood stream from some focus of infection. Good examples are the heavily infected vegetations on the heart valves in acute endocarditis, the thrombosed open blood sinuses of the septic puerperal uterus, and the bacteria-laden bone-marrow of acute osteomyelitis. When the focus is removed or even drained, the bacteria may rapidly disappear from the blood stream.

**PYEMIA.**—Pyemia is one step further in the septicemic process. Clumps of bacteria lodge in the tissues and set up secondary abscesses in the kidney, liver, myocardium, skin, etc. (Fig. 56.) The condition is usually caused by thrombi infected with pyogenic bacteria breaking up and being

discharged into the circulation, only to be arrested when they reach the capillaries of the lungs, the glomeruli, etc.

The *postmortem appearances* in streptococcal septicemia are important. Rigor mortis is slight or absent, and postmortem decomposition is rapid. The blood is fluid and dark, and does not coagulate. Owing to hemolysis of the red blood cells the lining of the heart and large vessels is stained red, and jaundice may have been apparent during life. The heart is dilated, and the myocardium and muscles are friable and flabby. The spleen is enlarged, soft, and friable, a condition known as acute splenic enlargement. The walls of the capillaries are injured, so that there are petechial hemorrhages in such serous membranes as the pleura, pericardium, and endocardium. Many of these signs may be absent, so that in some cases the postmortem diagnosis of septicemia may present great difficulty to the pathologist. In pyemia in addition to the usual lesions of septicemia small yellow abscesses are present in the lungs, heart, kidney, and other organs, usually just under the surface.

**TOXEMIA.**—In septicemia and pyemia many organs show evidence of the action of toxins. These changes may be equally well marked even when no microorganisms have entered the blood stream. Diphtheria is an excellent example. Here the bacteria remain in the mucous membrane of the throat, but profound toxic changes are found in the heart, liver, and kidneys. These changes are degenerative in character, ranging from cloudy swelling and fatty degeneration to necrosis and disintegration of the cells. In toxemias of long duration amyloid degeneration may develop.

**Our Present Concept of Resistance.**—Although our understanding of these matters is but that of children, despite the use of a multitude of high-sounding words (at least so it appears to the writer), we can yet express some general ideas as to why some persons resist infection or quickly recover from it, while others do not. Resistance to infection depends upon three great factors: (1) humoral antibodies, (2) phagocytosis, and (3) the immunological (*i. e.*, chemical) behavior of certain tissue cells. The humoral and cellular forces work hand in hand, and the background of all the antibodies is formed by the cells of the reticulo-endothelial system.

Of the *antibodies* the most important appear to be antitoxins, bacteriolysins, and opsonins. Antitoxins do not rid the body of infection, but they cause the symptoms to clear up. Bacteriolysins (immune bodies) do not act directly on the bacteria, but merely play the part of an amboceptor whose hands join together the complement and the germ, to the destruction of the latter. The patient must therefore have enough of the all-important complement as well as an abundance of immune bodies if he is to recover. Opsonins must be present to sensitize the bacteria, so that these may be devoured by the phagocytes. The important part which the antibodies (opsonins and agglutinins) play in the localization of infection has already been considered. They serve to detain the invading bacteria until the leucocytes can collect in sufficient numbers at the site of infection to make their presence felt.

The *phagocytes* are not merely the polymorphonuclear leucocytes, although these form the first line of defense. Of equal importance are the macrophages of the tissues, derived in turn from the reticulo-endothelial

system. The fixed cells of this system play an important rôle in removing bacteria circulating in the blood. Vast numbers of organisms may be injected into the blood stream, but they rapidly disappear and are found in the reticulo-endothelial filters of the liver, spleen, bone-marrow, and lungs. Here also the humoral factor must not be overlooked. If a large dose of pneumococci is injected into the blood stream of a rabbit (a highly susceptible animal), a blood culture fifteen minutes later will show enormous numbers of organisms, but if antipneumococcus serum is injected into another vein at the same time the blood will be found to be sterile at the end of fifteen minutes. The sensitized bacteria are taken up partly by the circulating phagocytes, partly by the fixed reticulo-endothelial cells. This can be shown in the case of the liver by perfusing the liver with pneumococci suspended in saline solution or normal serum. None are retained. When a minute quantity of immune serum is added, there is complete retention of bacteria by the liver. These experimental observations on the removal of bacteria from the blood have been confirmed in man. Immediately after curettage for a septic abortion the blood may be loaded with bacteria, but there may be none 15 minutes later.

The factor of *tissue immunity* is perhaps the most important, although the hardest to understand. It provides the reason why some animals simply cannot be infected by microorganisms which are highly pathogenic to animals of another species. If a toxin or a virus has no chemical affinity for a cell, it cannot injure it, no matter in what quantity it may be present.

## ALLERGY

The body tends to protect itself against bacterial infection by certain processes which may be grouped under the common heading of immunity. But during the development of immunity there may appear a very different and indeed opposite type of reaction, namely, hypersensitiveness. This reaction is a hypersensitiveness to the *bacterial protein*, and an equally marked hypersensitiveness may be developed against any foreign protein (horse serum, egg albumen) which may be injected. The first injection produces no evident effect, but a second injection is followed by the development of striking and often dramatic phenomena which may be local or general in their manifestations. The interval between the two injections must be of a certain duration, at least a week or ten days, and it may be noted that this corresponds to the incubation period of many infectious diseases, *i. e.*, the time interval between the initial infection and the development of the tissue changes which produce the clinical phenomena of the disease. The condition of hypersensitivity is known as allergy, which means altered reactivity. Unfortunately the term has become one of the most abused in medicine. The factor best calculated to produce it is a chronic low-grade infection.

ANAPHYLAXIS is a form of hypersensitiveness which differs from and yet is related to allergy. In allergy the reaction is a necrotizing, inflammatory one, whereas in anaphylaxis it is a musculo-spasmodic one. Anaphylaxis has been studied for the most part in the experimental animal, but it also has its human counterpart.

Its principal manifestation is a spasmodic contraction of smooth muscle, chiefly of bronchioles and certain blood vessels, as a result of which the animal passes into a condition of anaphylactic shock which may result in death. It is above all a hypersensitiveness of smooth muscle. Human anaphylaxis is much less striking, because man is, fortunately, far less sensitive than the guinea-pig. A person may, however, become sensitized against horse serum (diphtheria and other antitoxins), so that a second injection may be followed by symptoms of anaphylactic shock and death.

Most of the experimental work has been done with non-bacterial proteins. As long ago as 1903 Arthus showed that when horse serum was injected into the skin of a rabbit which had been previously sensitized by injections of the same serum, a violent local reaction was produced, characterized by marked inflammation and necrosis and sloughing of tissue. This allergic inflammation with necrosis is known as the *Arthus phenomenon*. The essence of the reaction and, indeed, of allergy in general lies in the fact that the tissues are locally damaged and killed by an amount of protein which is harmless to the normal body. The injections need not be given at the same place; the first may be given intraperitoneally and the final one into the skin. It is evident that all the tissues become sensitized, and the allergic reaction is an antigen-antibody reaction in the cell itself.

Bacterial allergy is very similar in its reaction to the Arthus phenomenon, although the hypersensitive state cannot be transferred passively to a normal animal. It appears probable that in many, if not in all bacterial infections, hypersensitiveness develops *pari passu* with the development of immunity. Many destructive lesions which in the past have been attributed to the action of bacterial poisons are in reality due to hypersensitiveness to the bacterial proteins, although it must be admitted that allergy is a term often used to give a touch of mystification to ignorance. That the reaction is essentially a cellular one independent of circulating antibody is shown by the observations of Rich and Lewis on cells isolated from an animal rendered allergic to tuberculin and grown in tissue culture. When a minute amount of tuberculin is added to this allergic culture, the same tissue destruction and necrosis occurs which is seen in the living animal.

The *Shwartzman phenomenon* is a local tissue reactivity to bacterial filtrates. Shwartzman has shown that if a bacterial filtrate is injected into the skin, and the same filtrate is injected intravenously twenty-four hours later, a severe hemorrhagic and necrotizing inflammation develops at the site of the local injection. The preparing injection produces only a slight reaction. It may be made into the parenchyma of an organ such as the stomach or a joint. It can even be made into the vascular system of an organ, *e. g.*, injection into the renal artery after the renal vein has been clamped for five minutes. Lesions in the kidney can be produced when the preparing injection is made into the general circulation, probably because of the greater permeability of the glomerular capillaries. Renal lesions have developed as the result of a single intravenous injection in pregnant animals; this may possibly explain the diffuse symmetrical necrosis of the kidneys in eclampsia if pregnancy is regarded as a state of generalized increased reactivity.

The first change is marked venous and capillary dilatation and engorgement, soon followed by severe hemorrhage, edema, and intense infiltration with leucocytes. The veins and capillaries are filled with thrombi, amorphous granular masses probably consisting of platelets. A large central area of necrosis develops in the affected skin or organ. It is possible that some hitherto mysterious inflammatory lesions may find their explanation in the Shwartzman phenomenon.

**ALLERGIC INFLAMMATION.**—There can be no doubt of the existence of allergic inflammation, a type of tissue response to the local interaction of antigen and antibody. This can be demonstrated in the experimental animal. It is more than probable that a number of human inflammations

of uncertain nature and etiology are examples of a similar reaction. The general characteristics of allergic inflammation are acute onset, necrotizing arteritis, focal necrosis, and an inflammatory exudate mainly mononuclear in type, often with numerous eosinophils. Of particular significance is the absence of bacteria. Examples of conditions which may be allergic in nature are bronchial asthma, rheumatic fever, glomerulonephritis, periarteritis nodosa, Buerger's disease, and disseminated lupus erythematosus. When we come to study these conditions we shall find most or all of the above-mentioned features. It will be noticed that in most of them (including glomerulonephritis) the main tissue involved is part of the vascular system. In periarteritis nodosa the vascular lesions are remarkably similar to those seen in serum sickness in the experimental animal and in the rare cases observed in man (Rich). Fibrinoid necrosis of the arterioles is always suggestive of an allergic basis, and the walls of the vessels are often infiltrated with inflammatory cells.

**SULPHONAMIDE ALLERGY** deserves special mention. In 1917 Landsteiner showed that simple chemical compounds could become conjugated with serum proteins; they could thus become antigenic in character and capable of exciting an allergic reaction. This is true of the sulphonamide compounds, and it is now common knowledge that these substances may in certain hypersensitive persons produce toxic symptoms which are evidently allergic in character. The hypersensitivity is usually acquired as a result of previous exposure to the drugs, but it may be inborn. The worst offender is sulphathiazole. The clinical manifestations are fever, chill, a skin eruption, and failing renal function with anuria about a week after the administration of sulphonamides. The principal lesions are in the kidney, liver and heart, but almost any organ in the body may be involved, and the lesions are often widespread. They fall into the following groups: (1) focal necrosis associated with cellular infiltration, often amounting to a granulomatous reaction, the chief cells being histiocytes, lymphocytes, plasma cells, and eosinophils; (2) necrotizing arteritis similar to that seen in periarteritis nodosa; (3) severe parenchymatous degeneration in the liver and kidneys. More, McMillan and Duff, in a careful study of 22 cases, emphasize that all the lesions combine necrosis with activity of the reticulo-endothelial system; they describe and illustrate a peculiar necrosis of the splenic trabeculae. An acute interstitial myocarditis may cause death in some cases.

#### ADDITIONAL READING

- Allergic Inflammation.** RICH: Bull. Johns Hopkins Hosp., 1942, 71, 123.  
**Bacterial Invasiveness.** CHAIN AND DUTHIE: Brit. J. Exper. Path., 1940, 21, 324.  
 DURAN-REYNALS: J. Exper. Med., 1933, 58, 161.  
**Inflammation and Infection.** KETTLE: Lancet, 1927, 1, 1169, 1225.  
**Localization of Infection.** MENKIN: Arch. Path., 1931, 12, 802. RICH: Bull. Johns Hopkins Hosp., 1933, 52, 203.  
**Removal of Bacteria from Circulation.** CANNON, SULLIVAN, AND NECKERMANN: J. Exper. Med., 1932, 55, 121.  
**Sterilizing Power of the Skin.** ARNOLD AND BART: Am. J. Hyg., 1934, 19, 217.  
**Sulphonamide Inflammation.** BLACK-SCHAFER: Arch. Path., 1945, 39, 301. FRENCH: Am. J. Path., 1946, 22, 679. HARTROFT: Canad. Med. Assn. J., 1944, 51, 23. LICHTENSTEIN AND FOX: Am. J. Path., 1946, 22, 665. MERKEL AND CRAWFORD: J. A. M. A., 1942, 119, 770. MORE, *et al*: Am. J. Path., 1946, 22, 703. SIMON: Am. J. Med. Sci., 1943, 205, 439.

## Chapter

## 7

### BACTERIAL INFECTIONS

In this chapter will be considered some of the diseases produced by pathogenic microorganisms. Many of these will be described fully in the section on Special Pathology in connection with the organs principally affected (pneumonia, dysentery, etc.). In such cases the condition will only be mentioned here in passing. In others the lesions affect many organs (tuberculosis), or the infection may be general rather than localized (the infectious fevers). These conditions will be considered here more fully. No attempt is made to give bacteriological detail, as that would merely usurp the function of a text on bacteriology, but a few of the principal features of the microorganisms will be mentioned in order to recall them to the reader's mind.

#### STAPHYLOCOCCAL INFECTIONS

The staphylococcus is a pyogenic organism, and its action as a pus producer has already been described in connection with inflammation and suppuration. It occurs normally on the skin, and is prone to produce skin infections, entering through cracks, abrasions, or even by way of the hair follicles. In staphylococcal lesions of deeper organs (kidney, bone) an active skin infection (boil) or one which has recently healed can usually be found. In human blood there are natural agglutinins to the staphylococcus, so that when the tissues are invaded the organisms tend to adhere together and to the surrounding structures. For this reason staphylococcal lesions are more likely to be localized than diffuse. The cocci produce a coagulase, causing marked formation of fibrin. This further limits the spread by blocking paths of dissemination, as shown by the fact that when a dye is injected it does not spread along the lymphatics. In all of these respects staphylococci differ from streptococci, which tend to invade mucous membranes, and produce a fibrinolysis that breaks down the defense barrier. Some strains of staphylococci, however, produce a soluble "spreading factor" which markedly increases the permeability of the tissues (Duran-Reynals' phenomenon). Under appropriate environmental conditions, of which the hydrogen-ion concentration is one of the most important, certain strains have the power of forming an extremely powerful exotoxin in culture. Broth filtrates are found to produce three effects which may be called the hemolytic, the necrotizing, and the killing. Injection of a small amount of toxin into the skin of the animal results in marked necrosis. The killing power of the toxin is its most striking characteristic; an extremely small quantity injected intravenously leads to death in a few min-

utes. The tragedy at Bundaberg in Queensland, when 12 out of 21 children, injected with diphtheria toxin-antitoxin mixture, died in the course of a few hours was due to contamination of the mixture with a toxigenic strain of staphylococci. The toxin can be detoxicated by the addition of formalin; the resulting product is called toxoid, and this still retains its antigenic property. Superficial staphylococcal infections apparently do not provide an adequate antigenic stimulus, for persons with repeated boils may show no increase of antitoxin in the blood.

**BOTRYOMYCOSIS.**—This is a peculiar form of staphylococcal infection, common enough in horses, cattle and pigs, but very rarely observed in man. The lesions, which show chronic suppuration and extensive fibrosis, involve chiefly the liver, and more rarely the genitalia and bones. In the liver there are large inflammatory masses containing many small cavities filled with pus. The characteristic feature is the presence of large colonies of staphylococci embedded in the pus cells and held together by a network of fibrin. Club-shaped masses project from the colonies in a manner reminiscent of the clubs in actinomycosis, so that the disease is also known as staphylococcal actinophytosis. Granulomatous lesions with epithelial and giant cells may be seen in the connective tissue (Berger).

## STREPTOCOCCAL INFECTIONS

The streptococcus is usually a pyogenic organism and produces lesions which in general resemble those of the staphylococcus, but they tend to be more diffuse and spreading and are characterized by cellulitis, lymphangitis and lymphadenitis. The streptococcus unlike the staphylococcus may invade a surface without producing a local lesion. A mere pin prick may introduce streptococci which cause a fatal septicemia. Other portals of entry are throat infections, tonsillitis, middle-ear inflammation, an infected tooth socket, puerperal uterine sepsis, etc. Some of the most dangerous infections are those of the hands of the surgeon or pathologist (owing to the heightened virulence caused by passage through the body of the patient) and puerperal infection (exhaustion of the patient, anemia, raw areas, etc.).

*Streptococcal fevers* are in general more serious than those caused by staphylococci. Endocarditis, puerperal fever, scarlet fever, and erysipelas are particular examples, the last-named being considered below. Streptococci often complicate other infections and may be the cause of a fatal termination (influenza, etc.). Streptococcal septicemia is marked by rigors, high fever, a large spleen (though this is often too soft to be felt), diarrhea, and the presence of albumin and red blood cells in the urine. There is no infectious disease in which anemia may develop so rapidly; the hemoglobin may fall to 30 or even 20 per cent.

The metastases differ from those of staphylococcal fever, the serous membranes being mostly involved in accordance with the diffuse nature of the infection. There may be suppuration of the joints, pleura, pericardium, meninges, and peritoneum. There is not much tendency to local abscess formation unless infected emboli (endocarditis, puerperal sepsis) are circulating in the blood.

It has long been known that non-suppurative lesions may follow at varying intervals of time such hemolytic streptococcal infections as scarlet



fever, erysipelas and puerperal infection. They have been called *Nachkrankheiten* by German investigators. They are most marked in cases with persistent bacteremia. These late tissue reactions are more prominent and more frequent ten days or more after the onset of the infection. For these reasons it has been suggested that they represent an antigen-antibody reaction (Mallory and Keefer). The lesions are most marked in the heart and kidneys, but they may occur in most of the viscera. The focal cellular reaction is predominantly mononuclear rather than polymorphonuclear.

**ERYSIPELAS.**—This is an acute inflammation of the lymphatics of the skin caused by hemolytic streptococci with marked erythrogenic (rash-producing) power which enter through some break in the surface, often very minute. The face or scalp is the usual site, and it is probable that the starting-point is often a latent infection of the nose or nasal sinuses. The common idea that erysipelas is an extremely infectious condition is wrong. Unless there is a discharge from the skin there is no danger of infection. From the site of inoculation the infection spreads outward, producing a bright red indurated area with a characteristically sharp margin. Just beyond this margin the lymph spaces are crowded with streptococci. There is a curious absence of suppuration, the inflammatory cells which crowd the tissue being almost all lymphocytes or mononuclears. In the more severe cases the deeper tissues may be involved, with thrombosis, cellulitis, and suppuration. General constitutional symptoms such as high fever and leucocytosis are not due to a blood invasion by the streptococci but to the absorption of toxins produced locally. An erythrogenic antitoxin of value has been prepared against the streptococcus of erysipelas.

**Scarlet Fever.**—Scarlet fever or scarlatina is an acute infectious fever caused by a specific strain of streptococcus, characterized by a high temperature, sore throat, and widespread rash, followed by nephritis, otitis media, and suppuration of the cervical lymph nodes.

It has long been suspected that hemolytic streptococci had some causal relationship to scarlet fever, for these organisms were commonly found in the throat lesions, but there were difficulties in the way. Scarlet fever was apparently a toxic disease like diphtheria, but the streptococcus was not known to produce an exogenous toxin. The life-long immunity which commonly follows an attack did not correspond with what was known of other streptococcal infections. Finally there was the difficulty that the disease could not be reproduced in the lower animals.

The problem was solved by the contributions of many workers, but the coping stone was laid by George and Gladys Dick in 1923. These workers showed that hemolytic streptococci from scarlatinal throats produced a toxin which when injected into the skin of persons who had never had scarlet fever caused an erythematous reaction (Dick test). The disease is now regarded as a local infection of the throat by a specific strain of hemolytic streptococcus, with distant toxic manifestations (rash, nephritis, etc.). Unlike diphtheria, the germ of scarlet fever can invade the blood and set up suppurative lesions in various organs.

**SYMPTOMS.**—The *throat* is always inflamed, but the larynx does not share in the inflammation. There may be an angina, an extremely severe inflammation with tissue destruction and the formation of a membrane. In these cases middle-ear suppuration is very likely to occur owing to spread of the infection along the Eustachian tube. Swelling of the *lymph nodes* is constant, and indeed swelling of the lymphoid tissue throughout the body, so that the name of lymphatic fever has been suggested. There may be suppuration and abscess formation in the lymph nodes of the neck. The *rash* is of a generalized punctiform type. The mucous

membrane of the tongue shows a similar condition so that it has a strawberry appearance (strawberry tongue). *Albuminuria* is common, but this must be distinguished from true nephritis which when it occurs comes on during convalescence. The *nephritis* is marked by edema of the face which becomes pale and puffy, by a rapidly developing general anasarca, and by oliguria, albuminuria, and blood and casts in the urine. The blood in scarlet fever shows a well-marked leucocytosis.

**LESIONS.**—The lesions are in the main toxic in nature, but some of the complications may be suppurative owing to streptococcal invasion. The principal lesions are found in the skin, tongue, throat, and lymphoid structures. In the *skin* the vessels of the dermis are enormously dilated. This is due to vascular paralysis from the action of the toxin, and is not a true inflammatory reaction. There is no change in the epidermis at first, but later (fifth to tenth day) the epithelial cells are separated by an infiltration of polymorphonuclear leucocytes. When the rash has faded there is much desquamation, and the epithelium accordingly shows many cells undergoing mitosis. The *tongue* shows the same changes as the skin.

The *lymphoid tissue* of the lymph nodes, both superficial and deep, the spleen, tonsils, liver, etc., shows hyperplasia. The germinal centers are swollen, and the sinuses dilated and filled with endothelial cells. The *heart* shows cloudy swelling and fatty degeneration. *Toxic lesions* also occur in the liver, kidney, adrenal, and spleen. These take the form of injury to the vessel walls with secondary infiltration by mononuclear cells into the surrounding tissue.

*Nephritis* is a common complication of convalescence, coming on in the third week. It is an acute glomerulonephritis with the usual glomerular and tubular changes found in that condition. No streptococci are found in the kidney, so that the nephritis is apparently toxic in origin. Rather rarely there is quite a different type of lesion, an acute interstitial infiltration with polymorphonuclear leucocytes. These lesions are described more fully in connection with Bright's disease. The prognosis of scarlatinal nephritis is remarkably good if the patient is kept in bed. It usually clears up in from three to six weeks, and uremia is quite uncommon.

## RHEUMATIC FEVER

Rheumatic fever is a widespread infection of fibrous tissues affecting the joints, the heart, and other organs. It resembles syphilis in being a chronic, perivascular, long-continued infection with ups and downs. The first attack usually occurs in childhood. While in the adult it is the joint lesions which dominate the picture, in children these may be negligible and, indeed, overlooked, so that in later years it may not be possible to get a past history of rheumatic fever, but the heart always suffers. It is of children in particular that the saying holds true that "rheumatism is a disease which licks the joints, but bites the heart."

**ETIOLOGY.**—The cause of rheumatic fever is still uncertain. Some observers think that it is a specific strain of streptococcus, while others believe that a number of different strains of non-hemolytic streptococci may be responsible. The difficulty is to demonstrate the organisms in the lesions. Even when present they are not numerous, and the fluid

from the joints is nearly always sterile. Green examined the valvular lesions bacteriologically in 9 cases of acute rheumatic endocarditis. In 8 of these he succeeded in culturing *Streptococcus hemolyticus* from the valves, and *Streptococcus viridans* in one. No bacteria were found in the heart's blood, nor were they obtained from the valves unless gross lesions were present. In 5 of the 9 cases the same strain of *Streptococcus hemolyticus* was cultured from the throat during life as was present in the valvular lesions.

The great scarcity of organisms in even the most acute lesions is to be explained on a basis of allergy. The tissues become sensitized to the bacterial protein, and it is the antigen-antibody reaction in the tissues, in the ground substance in particular, which is responsible for the production of the lesions. In man the focus of infection is probably in the mouth and naso-pharynx (teeth, tonsils, nasal sinuses). The belief in the allergic basis of rheumatic fever is strengthened by the observation of Rich and Gregory that rabbits subjected to experimental serum sickness develop lesions similar to those of rheumatic carditis.

Coburn points out that the incidence of rheumatic fever parallels in a striking manner the incidence of hemolytic streptococci in the throat and also the incidence of streptococcal diseases such as scarlet fever in which the primary infection is in the upper part of the respiratory tract. This incidence is affected to a marked degree by climate. Both are common in cold, damp climates, but are rare in many parts of the tropics. Both are common in the children of the poor, but rare in the children of the wealthy. A child who suffers from recurring attacks of rheumatic fever and streptococcal sore throat in the slums of New York remains well when transported to South America. In the western part of the United States rheumatic heart disease is about ten times commoner in school children living in regions near the Canadian border than in those from regions near the Mexican border. From these observations Coburn concludes that the infectious agent which *initiates* the rheumatic process is *Streptococcus hemolyticus*, but that some other factor as yet elusive is required to complete the picture. This factor may be a vitamin or other food deficiency.

We may sum up the matter by saying that there is a considerable mass of evidence in favor of a streptococcus (not necessarily a single specific strain) being the causal agent in rheumatic fever, the comparative absence of organisms in the lesions being explained on an allergic basis. The original lesions in the heart, etc., must be due to the presence of bacteria in the tissues, but a condition of hypersensitiveness is maintained by a focal infection in the throat. In addition to the streptococcus, some additional factor is probably needed, and it is possible that in many cases this accessory factor may be a food deficiency.

**THE LESIONS.**—The fibrous tissues and certain serous membranes are attacked in rheumatic fever. A characteristic lesion is produced known as the Aschoff body. This corresponds to the miliary tubercle of tuberculosis. It is a proliferative lesion. Even earlier, as Klinge pointed out, is *fibrinoid degeneration or necrosis*, a change in the ground substance and collagen as a result of which the connective tissue assumes a lattice-like appearance with some of the staining characteristics of fibrin. This change is best seen

in the subcutaneous nodules, not in the cardiac lesions. In addition there is an exudative lesion, an outpouring of serum, most marked in the joints. The remarkable effect of salicylates on the symptoms of rheumatic fever are well known. The salicylates interfere with the spreading effect of hyaluronidase, just as does cortisone. It is possible that they act through the anterior lobe of the pituitary and the adrenal cortex, for they are without effect on hyaluronidase after adrenalectomy or hypophysectomy.

The *Aschoff body* is seen in most typical form in the interstitial tissue of the myocardium. (Fig. 57.) It is the result mainly of proliferation, but the exudative element is also present. It may be just visible to the naked eye, but is often invisible. In the heart it is oval or lemon-shaped. It is paravascular in distribution, being situated in relation to the adventitia of the small arteries, but it is at one side of the vessel and does not surround it.

There are four components of the Aschoff nodule. (1) A center of necrotic material, often quite small in amount. (2) Aschoff cells. These form the characteristic feature. They are large cells of the epithelioid type, usually multinucleated. They are probably derived from the histiocytes, members of the reticulo-endothelial system. Many are really giant cells, but they have seldom more than six or seven vesicular nuclei, and resemble the giant cells of Hodgkin's disease rather than those of tuberculosis. (3) Lymphocytes and plasma cells, with an occasional polymorphonuclear leucocyte. (4) Proliferation of fibroblasts with subsequent fibrosis. Edema, thrombosis, and swelling of the endothelium of the small vessels may also be present. Gross and Ehrlich have described what they call the life cycle of the Aschoff body, showing that a progressive series of changes can be recognized. Swelling of the collagen is a conspicuous feature of the earliest lesion. So also is the formation of a network of argentophilic reticulum fibers, as first pointed out by Klinge. For the details of the life cycle the original paper should be consulted.

The special rheumatic lesions of the *heart* will be considered in connection with Diseases of the Heart. There is a pancarditis (myocarditis, endocarditis, pericarditis), and these "bites" in the heart are by far the most important part of the disease. Rheumatic fever is the chief cause of chronic valvular disease.

The *pharynx* may be regarded as the site of the primary lesion from which the rest of the body is infected. A sore throat frequently precedes or is associated with the onset of an attack of rheumatic fever. Fraser has found rheumatic nodules in the pharyngeal tissues during an acute



FIG. 57. — Aschoff body in myocardium. The oval body separates the heart muscle fibers.

attack. Similar nodules were present in the neighborhood of the tonsils, in the lingual and laryngeal tonsils, and in the upper deep cervical lymph nodes.

In the *skin* the rheumatic lesion is known as the subcutaneous nodule. It occurs in the deep fascia, especially over bony prominences, and is composed of a group of Aschoff bodies. The general structure is the same though the outline is more indefinite.

In the *joints* the lesion is exudative, and it is to the sudden exudation in a tissue supplied so abundantly with small sensory nerves that the pain is due. Proliferative and vascular changes are also found in the synovial membrane, the capsule and the periarticular fibrous tissue. It is possible that the infective form of chronic arthritis may prove to be related to rheumatic fever. At least it appears to be a joint manifestation of a low-grade streptococcal infection.

The *brain* may be affected and the patient suffers from chorea (St. Vitus' dance). The lesions are in no way distinctive. There are perivascular collections of round cells, thrombosis, and endothelial proliferation in the meninges, cerebral cortex, and corpus striatum. The condition is a rheumatic meningoencephalitis.

*Rheumatic Pneumonia*.—Patients dying in the acute stage may show pneumonic consolidation, the lung having a peculiar India rubber consistence. There may be true Aschoff nodules in the fibrous septa, an interstitial infiltration of large, often multinucleated, cells, or areas of acute focal necrosis. (Gouley and Eiman.) *Pleural lesions* have been described. In many of the fatal cases there is a pleurisy, at first dry and later with effusion. There is metaplasia of the endothelium and inflammation in the subpleural layers.

*Rheumatic peritonitis* occasionally occurs. Rhea found plaques of inflammation on the parietal peritoneum and nodules in the subperitoneal connective tissue in a case of rheumatic carditis. The microscopic picture was identical with that in the heart except that the lesions were diffuse rather than focal.

## PNEUMOCOCCAL INFECTIONS

The principal disease caused by the pneumococcus is lobar pneumonia. This is described in connection with diseases of the lungs. The pneumococcus is a pyogenic organism, but it also has a marked ability to excite the formation of fibrin. The pulmonary alveoli are therefore filled with an inflammatory exudate composed mainly of pus cells and fibrin. Pleurisy is an invariable and empyema a less common accompaniment of lobar pneumonia.

Other lesions caused by pneumococci are endocarditis, pericarditis, peritonitis (especially in children), arthritis, meningitis, middle-ear supuration, infection of the nasal sinuses, etc. These conditions will be described in their proper place.

## BACILLUS TYPHOSUS INFECTION

*Bacillus typhosus* is identical morphologically with *Bacillus coli*. It is Gram-negative and actively motile. The two organisms can readily be distinguished by their reaction on lactose in the presence of an indicator. *Bacillus coli* ferments the

sugar with the formation of acid which changes the color of the indicator; *Bacillus typhosus* has no action on lactose, it is a non-lactose fermenter, so that the color remains unchanged. The same is true of the paratyphoid bacilli, which behave in the same way and produce the same lesions as the typhoid bacillus, so that they may be considered together. The final proof of the identity of a member of this group is afforded by producing agglutination of the bacilli by a specific antiserum in high dilution.

**INFECTION.**—The source of fresh infection is always human, either a patient suffering from the disease or a healthy carrier. The infection is alimentary, and is conveyed by infected water, milk or food, or by direct contagion. Epidemics can usually be traced to either water or milk infection. The bacilli do not multiply to any degree in water, but they multiply rapidly in milk, so that a milk-borne epidemic is more violent and explosive due to the massive infection. Food and milk may be infected by the contaminated fingers of a carrier (cook, dairyman) or of a nurse who has been looking after a typhoid patient. Flies may convey the infection from uncovered dejecta to uncovered food. Water infection is usually due to sewage contamination.

One of the chief sources of danger is the *chronic carrier*. A patient who recovers from the disease may continue to harbor the bacilli in his body, which are discharged for years usually in the stools, sometimes in the urine. A carrier is only dangerous when his occupation entails the handling of food or milk or if the excreta are not properly disposed of (camp life, armies in the field, etc.).

The portal of entry is usually supposed to be the lymphoid tissue of the small intestine where the earliest lesions occur, but there has always been a wide gap in our knowledge between the entry of the bacilli into the mouth and the development of symptoms of infection. It is impossible to see typhoid bacilli in any numbers in the lesions, except when a considerable interval has elapsed between death and autopsy, and yet they can usually be demonstrated by cultural methods. Goodpasture has shown that in early stages of the disease small Gram-negative bacilli, which appear to be typhoid bacilli, can be seen in large numbers in the cytoplasm of young plasma cells in the lymphoid follicles of the ileum, and he suggests that the young plasma cell acts as an essential cellular host for the bacilli which multiply within it. The abdominal lymph nodes draining the bowel are infected from the beginning and give a pure culture of the bacillus. The bacilli multiply in the lymph nodes during the period of incubation; they then pass by the thoracic duct to the blood stream and are liberated into the blood stream at the end of the incubation period; many of them are broken down and their endotoxins liberated. It is these toxins which cause the general symptoms and some of the lesions (focal necrosis of liver, Zenker's degeneration of muscle).

**SYMPTOMS.**—The symptoms are partly general, partly intestinal, partly hemopoietic. The general symptoms are fever, headache, malaise, lethargy, and a clouding of the mind which gives the name to the disease (*typhos*, a cloud). These symptoms are a manifestation of toxemia due to the action of bacteriolysis on the bacilli; they therefore become more pronounced as the disease progresses. Rose spots appear on the abdominal wall. Bronchitis and nose-bleeds may be early symptoms. The intestinal symptoms are abdominal discomfort, constipation or

diarrhea. The hemopoietic symptoms are enlargement of the spleen, leucopenia, and disappearance of the polymorphonuclear leucocytes and eosinophils.

**LESIONS.**—Typhoid fever is primarily an infection of the hemopoietic tissue, and in particular the lymphoid tissue of the intestine, the abdominal lymph nodes, the spleen, and the bone-marrow. As there is always a bacteremia any organ may be involved, but the most important lesion to add to the above is infection of the gall-bladder. The typhoid bacillus excites a peculiar cellular reaction which is quite characteristic, and unlike the suppurative reaction produced by its pyogenic cousins, the colon bacillus and the dysentery bacillus. There is an almost complete absence of polymorphonuclear leucocytes, their place being taken by large mononuclear phagocytes of the reticulo-endothelial system. (Fig. 58.) These phagocytes may contain lymphocytes, red blood cells, and other cell inclusions. (Fig. 59.)



FIG. 58.—The lesion of typhoid fever; a collection of large mononuclear cells.  $\times 600$ .

The lesion is productive rather than exudative in type. The red marrow is filled with these cells, to the exclusion of the polymorphonuclear and eosinophil leucocytes, thus explaining the leucopenia and the disappearance of polymorphonuclears and eosinophils.

The *intestinal lesions*, which are confined to the lymphoid tissue, are most marked in the lower part of the ileum, but may involve the greater part of the small intestine and also the colon. The Peyer's patches and the solitary follicles are crowded with the large mononuclear phagocytes, so that the lymphoid masses project above the surface. By the end of the first week these lesions become necrotic, the overlying mucosa forms a slough, and when this separates it leaves an ulcer. (Fig. 60.) The ulcers are round or irregularly oval with the long axis in the long axis of the bowel, since that is the direction of the Peyer's patches. In the cecum and colon the ulcers are smaller, owing to the smaller size of the solitary follicles.

Many are quite shallow, but the submucosa is often perforated, so that the floor of the ulcer is formed by the muscularis or even the peritoneum. There may be no ulcers, for the patient may die of toxemia before ulceration has time to take place. The number and size of the ulcers bear no relation to the severity of the disease. But the ulcers are accountable for the two complications which are responsible for a majority of the deaths, namely, hemorrhage and perforation. As the patient may have a deep ulcer and yet be only slightly ill, it follows that every case of typhoid must be treated with the greatest care. The ulcers heal with the formation of little or no

scar tissue. The ulcer is covered by a simple type of epithelium without the formation of new glands.

The *lymph nodes* of the mesentery are always involved, especially those which drain the lower ileum. Their sinuses are distended with large mononuclear phagocytes, and the nodes are therefore swollen and soft.

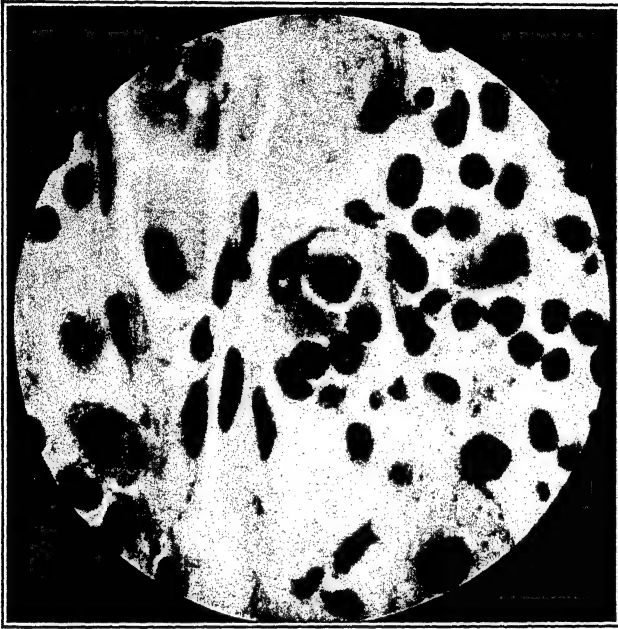


FIG. 59.—Typhoid macrophages. The one in the center contains a lymphocyte and four erythrocytes.  $\times 1000$ .



FIG. 60.—Typhoid ulcers of the bowel. A necrotic slough occupies the center of each lesion.

The *spleen* shows acute splenic swelling. It is moderately enlarged, usually weighing about 500 grams, deep red in color and very soft. Microscopically the usual collections of large mononuclear cells are seen with small areas of necrosis, but the most striking lesion is a crowding of the pulp with enormous numbers of red blood cells, so that it may seem to contain little but blood. The reason for this extreme congestion is not



clear, for it is not seen in the other lesions; possibly the masses of mononuclears obstruct the outflow from the sinuses so that they become overfilled with blood.

In the *liver* the typhoid lesion is focal necrosis. The lesion is really a combination of mononuclear proliferation and necrosis. The large mononuclears block the sinusoids and the liver cells become necrosed. The lesions are quite small and resemble miliary tubercles.

The *gall-bladder* is always infected, although the lesions are negligible. The bacilli live in the bile and pass down into the bowel, where they are most numerous in the duodenum. Most of the bacilli in the stools come from the gall-bladder, not from the ulcers in the bowel. They may continue to live in the gall-bladder after recovery and are excreted in the stools. Such a person is a typhoid carrier.

The *kidneys* show cloudy swelling and clumps of bacilli, so that bacilli often appear in the urine. A urinary carrier continues to discharge bacilli long after recovery.

The *lungs* may show bronchitis in the early stage and pneumonia (lobar or bronchopneumonic) later. The pneumonia is usually pneumococcal, but it is sometimes due to the typhoid bacillus.

The *heart* muscle is soft and swollen, and the blood-pressure low. The pulse is characteristically slow, and the pulse often dicrotic.

The *veins* are often thrombosed, especially the femoral and saphenous veins and the cerebral sinuses.

The *muscles* may show Zenker's degeneration, a hyaline change in which the fibers lose their transverse striations and are broken up into swollen hyaline masses. The chief sites are the lower part of the rectus abdominis, the diaphragm, and the thigh muscles. Rupture of the muscle may occur with hemorrhage. The condition, which is due to the toxins, may also occur in other infections.

The *bones* may show a chronic suppurative lesion, either abscess or periostitis, which may come on months or years later. The common sites are the tibia, sternum, ribs, and spine. The pus often contains living typhoid bacilli.

The *blood* shows a marked leucopenia (2000 to 5000 per c.mm.), with decrease in the polymorphonuclears and eosinophils (these may vanish) and an increase of large mononuclear cells.

THE RELATION OF SYMPTOMS TO LESIONS.—The general symptoms such as fever, headache, lethargy are due to the toxins which are liberated when the bacilli are broken down in the blood stream. The rose spots are caused by bacterial emboli in the skin capillaries. The enlargement of the spleen which forms one of the chief clinical pictures is due to the great accumulation of cells in the splenic pulp. The intestinal symptoms including hemorrhage and perforation are the result of the ulcers. The blood changes (leucopenia, disappearance of polymorphonuclears and eosinophils) are the direct result of the lesions in the bone-marrow. The carrier state is an indication that the constant infection of the gall-bladder has become chronic instead of clearing up.

LABORATORY AIDS IN DIAGNOSIS.—The four most valuable laboratory tests are: (1) blood culture, (2) the Widal test, (3) the demonstration of bacilli in the feces and the urine, and (4) the leucocyte count. *Blood culture* is positive at the beginning of the disease (the period of bacteremia) and during the first week. After that more and more bacilli are destroyed so that it becomes increasingly difficult to get a positive culture. The *Widal test* has a great reputation, but it has very real limitations and is less valuable now than formerly for the two reasons that many persons who have been inoculated against typhoid give a positive agglutination

reaction, and many cases of typhoid do not give a reaction until late in the disease, by which time the diagnosis is self-evident. After recovery the agglutinins persist for months, sometimes for years, while the agglutinins due to inoculation usually disappear in a few months, although they may reappear after a number of years as the result of some non-typhoid disease (*anamnesic reaction*). The Widal test is frequently negative in carriers. *Bacilli in the stools* are found more readily in carriers than in the active disease. They are most numerous in the third week, as by that time the bile is loaded with bacilli. The *urine* may contain bacilli in the third week. The *diazo reaction* in the urine is negatively pathognomonic, as it is present in practically every case, but is also found in other infective fevers, especially miliary tuberculosis, which may simulate typhoid. Culture of the *bile* obtained by *duodenal drainage* is one of the best methods of detecting a carrier. The peculiarities of the *leucocyte count* have already been described. For making an early diagnosis the two most valuable tests are blood culture and the leucocyte count.

## TUBERCULOSIS

Tuberculosis is a chronic inflammation caused by the tubercle bacillus. This thin curved rod, stained with difficulty and grown in artificial culture with still greater difficulty, was discovered by Robert Koch in 1882. Koch's discovery of the bacillus is one of the masterpieces of bacteriological research, for in the course of one year he found the organism, invented a culture medium on which it could be grown, and reproduced the disease in animals. Tuberculosis belongs to the group of the *infectious granulomata*, other members of which are syphilis, leprosy, actinomycosis, and other less common infections. The original meaning of the word was a new formation resembling granulation tissue. The resemblance to granulation tissue is fancied rather than real. A granuloma is an inflammatory mass consisting largely of epithelioid cells, as in tuberculosis, or of lymphocytes and plasma cells, as in syphilis, whilst in actinomycosis an added suppuration complicates the picture. The variations of tuberculosis are endless but they are merely the result of the interplay of the forces of destruction and repair. In man the tendency to repair is commonly greater than the destructive process, especially if the affected part such as the lung can be put at rest. Even though destruction may have proceeded for some time it may be followed by a remarkable degree of repair, so that in tuberculosis it cannot be said that "the struggle naught availeth, the labor and the wounds are vain." In this struggle the three factors to be considered are size of dose, immunity and allergy.

The disease is amazingly widespread, as is shown both by the tuberculin reaction and autopsy examination. The figures naturally vary in different countries, and the incidence is higher in large cities than in rural districts. Statistics compiled from the great centers and from the poorer class of the community showed that before the age of ten about 15 per cent, before the age of twenty from 30 to 60 per cent, and after middle life about 99 per cent of persons were infected. These figures were compiled from autopsy studies in the earlier part of this century. As a result of the campaign against tuberculosis a generation of children and young adults has grown up which has escaped primary infection and is negative to tuberculin. Thus in a school for nursing at Oslo 52 per cent of the entering students

were tuberculin-negative (Heimbeck). This has produced a great change in the disease picture.

The bacilli come from man or from the cow (milk). The bovine form of tuberculosis used to be of importance, particularly in Scotland where it was very prevalent owing to widespread infection of cattle. Inspection of herds and pasteurization of milk have reduced this form of infection to negligible proportions in most communities. Pulmonary tuberculosis is always due to human infection, but some cases of intestinal tuberculosis in children may be due to infection with the bovine type of bacillus.

**The Inflammatory Reaction.**—The reaction of the body to the tubercle bacillus varies considerably, depending on the following factors: (1) the species of animals, (2) the size of dose, (3) the question of whether the animal is tuberculosis-free or has already been infected. The influence of these factors will be discussed as we proceed. In spite of possible variations there is a standard type of reaction caused by a moderate dose of bacilli of unattenuated virulence in a susceptible species of animal which is infected for the first time. *Polymorphonuclear leucocytes* are the first to arrive in response to an injection of tubercle bacilli. They are actively phagocytic, but are unable to damage the bacilli which they engulf. They play a useful part, however, in focalizing the infection by preventing to some extent the drift of bacilli through the tissues. The response of the polymorphonuclears is very much more marked in a reinfection, *i. e.*, in the allergic inflammation of an already tuberculous animal. Their appearance is transitory, and within twenty-four hours they are replaced by *mononuclear cells*, also known as macrophages and monocytes.

These cells represent the essential reaction of the body to the tubercle bacillus, but it is to the fatty envelope of the bacillus that the response is made, for the same effect is obtained by the injection of lipid extracted from the bodies of the bacilli. In some of the experimental work they have been the first cells to arrive. Thus Fried found that the intratracheal injection of bacilli in the rabbit caused an amazingly rapid appearance of mononuclears. When the animal was killed one minute after the injection the cells had begun to appear and in the course of five minutes a definite primitive tubercle has been formed within the alveoli. The mononuclears are highly phagocytic members of the reticulo-endothelial system. The bacilli and also the polymorphonuclears containing bacilli are phagocytosed by the mononuclears, by which they are gradually broken down with dispersion of the lipid throughout the cytoplasm. This dispersion results in the transformation of the mononuclear into the *epithelioid cell* (epithelial-like), which is the most characteristic single feature of the tuberculous reaction. It is a large, pale cell with rather indistinct margins, the nucleus is large and vesicular, and the abundant cytoplasm often presents processes which pass from one cell to another to form an epithelioid reticulum. The epithelioid cell, then, may be regarded as a large mononuclear which has partially digested tubercle bacilli, and its distinctive cytoplasmic state seems to be the result of destruction of many bacilli with progressive emulsification of their lipid (Long, Lurie). The epithelioid cell is particularly rich in ascorbic acid (vitamin C), and it seems probable that this substance

is connected with the enzyme activity of the principal reactive cells. The lymphocytes of the tubercle do not contain any demonstrable ascorbic acid. It is evident that by the time the mononuclears have become transformed into epithelioid cells the bacilli have undergone extensive destruction. This explains the difficulty which is experienced in demonstrating bacilli in the ordinary type of lesion in man, in which they are few and far between and may only be found after prolonged search, although in acute fulminating lesions such as tuberculous caseous pneumonia they may be present in great numbers. The mononuclears do not always have the power of destroying the bacilli which they engulf. Thus in the rat the bacilli thrive and multiply within the phagocytes, and the latter also multiply with the remorselessness of a malignant growth, until finally the animal succumbs to the cellular accumulation.



FIG. 61.—A miliary tubercle in the lung, showing epithelioid cells, giant cells, and peripheral lymphocytes.  $\times 150$ .

*Giant cells* are formed by fusion of a number of epithelioid cells. They may attain a great size, and contain large numbers of nuclei, usually arranged either around the periphery or at one or both poles, but occasionally scattered through the cytoplasm. Medlar points out that the matrix of the cell is necrotic (caseous) from the beginning, and suggests that the peculiar arrangement of the nuclei at the periphery is due to the epithelioid cells surrounding a central piece of necrotic material. Giant cells are not formed until necrosis has occurred. They are found in small caseous areas or at the edge of larger areas. They often contain tubercle bacilli, and their function is to digest and remove dead tissue. They are foreign body giant

cells, and indicate that an active resistance is going on. Giant cells are very characteristic of tuberculosis, but they occur in other chronic inflammations (syphilis, actinomycosis), and they may be absent in the acuter forms of tuberculosis where resistance is low (tuberculous meningitis, etc.).

By the end of a week *lymphocytes* appear, and form a ring around the periphery of the lesion. They are small cells with dark nuclei, identical with the lymphocytes of the blood, but they are probably derived from the cells of the perivascular lymph sheath or other lymphoid structures. The lymphocytes are one of the principal sources of the gamma globulins which constitute the immune bodies.

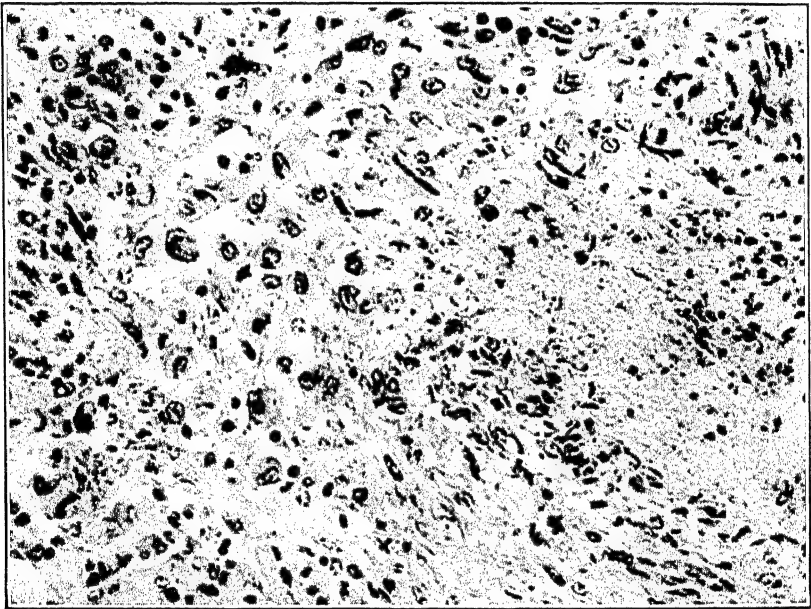


FIG. 62.—Tuberculous caseation, showing destruction of epithelioid cells.  $\times 325$ .

The small mass of newly-formed or newly-arrived cells constitutes a tiny translucent nodule visible to the naked eye and known as a *tubercle* or *miliary tubercle* (Fig. 61), since it is at first about the size of a millet seed, although it increases in size and several tubercles may fuse to form a larger mass. It is avascular, so that when the vessels of a tuberculous organ such as the lung are injected with a colored medium the tubercles stand out unstained. By the end of the second week *caseation* begins. This is a form of coagulation necrosis caused by the liberated protein fraction of the bacilli, and the intensity of the necrosis varies with the size of dose. Massive infection is likely to be accompanied by extensive caseation, as in acute tuberculous pneumonia. In the center of the tubercle the cells lose their outline, the nuclei disappear, and all structure is lost. (Fig. 62.) In the caseation of a syphilitic gumma the loss of structure may not be so complete, and some of the original outline may still be dimly discerned.

Other respects in which the two lesions may differ will be considered in connection with the gumma. The tubercle now presents a homogenous center staining red with eosin, a periphery of pale epithelioid cells with one or more giant cells, and an outer zone of dark blue lymphocytes.

There is a tendency for caseation to be followed by *softening* and liquefaction. Long points out that softening of the caseous tubercles is the key problem in tuberculosis, for were it not for softening the disease would be self-limited. Softening is associated with an extraordinary multiplication of the bacilli, so that when liquefied material is first discharged into a bronchus it has its maximum infecting power. From this it follows that acute fresh cavities discharging soft yellow lumps in the sputum are highly infective, while old chronic cavities are not an important source of infection. The precise cause of the softening is not understood.

The *prolonged use of streptomycin* has a profound effect on the progress of the disease (Auerback). This effect is most readily seen in surface lesions. Ulcers of the larynx, bronchial tract and intestine heal quickly. The contents of a cavity in the lung become inspissated, and later invaded by large numbers of neutrophils with resulting liquefaction and the formation of a cyst lined by squamous epithelium or fibrous tissue. Tubercle bacilli can still be demonstrated by staining, but not by culture nor animal inoculation.

The microscopic picture in tuberculosis is characteristic and readily recognized, but it must be borne in mind that a histological diagnosis of this disease is only presumptive. Other conditions may present a similar or even identical microscopic picture, for example sarcoidosis, coccidioidomycosis, histoplasmosis, brucellosis, and syphilis. In some of these (coccidioidomycosis, histoplasmosis) the etiologic agent can be found in the tissue, in others (brucellosis, syphilis) serologic tests are of value. Finally the sections may show only a picture of chronic inflammation with none of the features characteristic of tuberculosis, yet tubercle bacilli may be found on culture.

The *future history of the tubercle* varies greatly. (1) The experimental tubercle may resolve, disappear completely, and leave no trace. It is difficult to know if this occurs in man, but it probably does. The peritoneum may be found studded with tubercles, and yet if the abdomen is opened a year later the membrane may be smooth and normal. (2) A very common occurrence is for the caseous area to be surrounded by fibroblasts which form a fibrous capsule for the tubercle. Lime salts are deposited, and the calcified tubercle is said to be *healed*, but even in this quiescent lesion living bacilli may still lurk and can be demonstrated by animal inoculation. Reticulum may be present in tubercles composed entirely of epithelioid cells, and as reticulum is formed before connective tissue it is possible that the one may develop into the other, and that the mononuclears may take some part in the formation of collagen. (3) There may be a low-grade inflammation with the formation of *tuberculous granulation tissue* with many tubercles but no caseation. This is due to low virulence or high resistance, and is a rare form of the disease. This hyperplastic form is seen in the synovial membrane of joints, in the cecum, and occasionally in lymph nodes. (4) There may be *spread* of the infection, the bacilli being

carried by phagocytes through the tissues, giving rise to the formation of new tubercles which fuse together until large caseous areas are formed. (5) There may be an *acute inflammatory reaction* when the infection is virulent or massive, as seen in tuberculous meningitis and acute tuberculous pneumonia. This reaction, in place of being mainly productive, is essentially exudative in type and is characterized by a great outpouring of polymorphonuclear leucocytes and serum with, it may be, an abundant formation of fibrin. It is, however, not in first infections but in reinfections, sometimes called secondary infections, that the acute inflammatory reaction is seen to best advantage, and we may now turn to a consideration of the lesions which develop in the already tuberculous or allergic animal or man.

**Allergy and Immunity in Tuberculosis.**—Robert Koch realized the fundamental distinction between the reaction to the tubercle bacillus in a healthy animal and in one already infected with tuberculosis. If a healthy guinea-pig is inoculated with tubercle bacilli of low virulence a nodule forms by the end of two weeks. This breaks down and never heals, for the guinea-pig, in contradistinction to man, has no natural immunity. The regional lymph nodes become enlarged and caseous, as the bacilli are not retained at the site of inoculation. These tuberculous nodes form a valuable indication of the site of the primary infection. Involvement of the cervical nodes points to the tonsil as the portal of entry, the tracheo-bronchial nodes to the lung, the mesenteric nodes to the intestine. Swelling of the regional nodes is followed by general infection of the guinea-pig and death in two or three months.

The sequence of events following the inoculation of an animal which has previously been infected (reinfection) is very different. If a second dose is given a couple of weeks after the first, a local swelling appears in a few days; this breaks down and forms an ulcer, but the ulcer soon heals, and the regional lymph nodes are not enlarged (Koch phenomenon). This does not mean to say that they are not infected, for tubercles can be found in the nodes both in the experimental animal and in human reinfection, but most of the bacilli are retained at the site of inoculation, and those which succeed in reaching other parts find the soil unfavorable. The local reaction is an acute inflammatory one, it is more prompt in its appearance than in the healthy animal, and it is characterized by marked outpouring of polymorphonuclear leucocytes and plasma and above all by the occurrence of massive necrosis. It will be recognized that this reaction, which can be elicited by the injection of dead bacilli and tuberculin as well as by active infection, is a manifestation of the allergic inflammation which has already been studied in the previous chapter. It is dependent on the fact that the relatively bland tuberculoprotein acts in the allergic body as a powerful irritant and necrotizing poison.

The response to tuberculin is an allergic one. Tuberculin allergy may disappear after healing of a tuberculous lesion, although sensitivity is never lost in the presence of active infection. Children often change from a positive to a negative tuberculin reaction, but this rarely happens in adults.

The distinction between primary and secondary infection can be seen in the lungs. Using the regional lymph node involvement as an indicator of the primary lesion, Ghon was able by careful dissection to demonstrate

a primary lung lesion in over 90 per cent of children. This lesion, often called the *Ghon lesion* (Fig. 63), is a small caseous focus not more than 1 cm. in diameter, usually single, and situated in any part of the lung, but generally just under the pleura, and limited by a fibrous capsule. There is a larger caseous focus in the lymph nodes draining this area. It is of interest to note that Ghon's work was published in 1912 but the lesion known by his name was described in every detail in 1898 by a Paris physician, George Küss, who wrote a monograph on the subject which has been completely neglected. Very many of these lesions are healed, not only calcified but ossified. These lesions seldom contain viable tubercle bacilli, as shown by culture and guinea-pig inoculation (Feldman and Baggenstoss). The lesion may be healed, and yet the histological picture (cellular infiltration) may suggest active infection owing to the frequent presence of silica. If healing does not occur the child becomes allergic, the caseous lesions break down, and a rapidly spreading tuberculous pneumonia is apt to develop. The younger the child, the greater is the danger, for he has not had time to become immunized by repeated minimal infections. Therefore tuberculosis is especially dangerous in the first year of life. The child with primary infection either recovers or dies; he does not develop the chronic thick-walled cavities so characteristic of the disease in the adult.

A period of latency separates the primary and secondary types. The years from four to fourteen are almost free from fatal pulmonary tuberculosis.

When an adult develops tuberculosis he has already been infected in childhood. The one lesion is not a development of the other, but the result of a fresh infection from without, massive enough to break down the immunity produced by the primary lesion. As the adult lesion is of the secondary type it will become caseous and break down with the formation of a cavity. If the immunity due to the primary lesion has disappeared, reinfection will be of the nature of a first infection, and the patient may die of acute tuberculous pneumonia as in the first year of life. Owing to the greatly decreased incidence of childhood tuberculosis, primary tuberculosis in the adult is becoming increasingly common. The majority of



FIG. 63.—Active Ghon lesion. There is a subpleural caseous lesion in the lower lobe. The lymph nodes at the hilum are enlarged and caseous. Miliary tubercles are scattered through the lung, especially in the lower lobe. Some of the upper lobe has been removed. Death was due to general miliary tuberculosis.



persons infected for the first time in young adult life show few symptoms or serious effects, the disease being detected by routine tuberculin tests followed by roentgen-ray examination. If exposed a second time to infection, the patient will develop the usual lesions and symptoms of reinfection.

**Method of Infection.**—It is easy to infect a susceptible animal by three routes: inoculation, inhalation, and ingestion. In man we are interested not in possible routes, but in the method of common occurrence. Unless this is known prevention is not possible.

1. CONGENITAL INFECTION.—This may occur through the placenta, and tubercle bacilli have been found in the mesenteric lymph nodes of the newborn. It is so rare as to be negligible.

2. INFECTION THROUGH THE SKIN.—This is the chief method of infection in the experimental animal, but in man it is of little importance. A tuberculous lesion may develop on the hand of a nurse, surgeon, or pathologist (*verruca necrogenica*) through handling infected material. The infection may spread to the regional lymph nodes, but seldom gives rise to general tuberculosis.

3. INFECTION THROUGH THE GASTRO-INTESTINAL TRACT.—This route used to be of great importance in the days when a glass of milk was likely to contain many tubercle bacilli. The bovine type of infection was extremely common in the bowel and lymph nodes of children. Fortunately the pasteurization of milk has changed all that, so that infection through the gastro-intestinal tract is now of minimal importance.

4. INFECTION BY INHALATION.—This is the route by which the lungs are infected. There are three ways in which tubercle bacilli may be inhaled into the lungs.

*Droplet infection* is the common method in the adult. When a patient with active pulmonary tuberculosis coughs without shielding his mouth he sprays out innumerable tiny droplets of moisture containing millions of bacilli. In *dust infection* dried infected sputum is converted into dust which may be inhaled. Only minimal doses are likely to be inhaled in this way, and the result is more likely to be immunity than a breaking-down of resistance. *Mouth infection* may occur in children with contaminated hands, followed by inhalation of minute droplets of fluid.

**Method of Spread.**—The tubercle bacillus is non-motile, but it can be transported in the bodies of phagocytic cells. There are four chief methods of spread:

(1) By *direct extension*, the phagocytes carrying the bacilli into the lymph spaces of the surrounding tissue. (2) By the *lymphatics*. Tuberculosis is primarily an infection of lymphoid tissue. The bacilli may be detained by the lymph follicles of the mucosa (pharynx, bronchi, intestine) or by the regional lymph nodes. If they succeed in passing the Scylla of the lymph follicles and the Charybdis of the lymph nodes, they set out upon an Odyssey which may carry them far and wide, but always toward the lungs, for they pass by the thoracic duct to the venous blood stream and eventually the lungs and it may be the systemic circulation. (3) By the *blood stream*. Tuberculous bacilleemia is a natural accompaniment of tuberculous infection, because of the drainage of the lymphatics into the

venous system. This explains the occurrence of isolated lesions in almost any organ in the body. A bacillema must be distinguished from a *general miliary tuberculosis*, where enormous numbers of bacilli are poured into the blood stream. This may be due to heavy infection via the lymphatic-venous route, or a caseous lesion may ulcerate through the wall of a vein and flood the circulation with bacilli. The result is an acute toxic infection which may terminate in death in the course of a few weeks. Tiny miliary tubercles are found in every organ of the body, though these may hardly be visible to the naked eye. Generalized acute miliary tuberculosis used to be as rapid in course and as fatal in outcome as tuberculous meningitis. Streptomycin and isoniazid (isonicotinic acid hydrazide) have greatly lessened the gloom of the picture. Untreated miliary tuberculosis is not necessarily acutely fatal. A chronic miliary form is compatible with years of life and with recovery (Hoyle and Vaizey). Healed tubercles are found not only in the lungs, but also in the spleen, liver and other organs. (4) By the *natural passages*. Infection may spread along the bronchi, ureter and vas deferens. In these cases, however, it is difficult to be certain that the bacilli have not been carried along the lymphatics in the submucosa.

### SARCOIDOSIS

The condition known as Boeck's sarcoid is a granuloma with a microscopic picture resembling and easily mistaken for that of tuberculosis. It was first described by Jonathan Hutchison in 1869, but it has masqueraded under such a variety of names that it is only in recent years that it has come to command general attention. Perhaps the best descriptive name is that of *benign lymphogranuloma*, for clinically the lesions may simulate those of Hodgkin's disease, whilst histologically it may mimic tuberculosis. Sarcoid is certainly a misleading name. There is usually an astonishing absence of symptoms, the disease is seldom fatal, and autopsy reports are correspondingly rare. The condition appears to be particularly common in Scandinavian countries.

The diversity of lesions, or rather of organs involved, is remarkable. The chief tissues affected are the skin and lymph nodes, both superficial and deep, but there may be splenomegaly, hepatomegaly, and lesions of the lung, myocardium, pancreas, testis, tonsil, digits, parotid and lachrymal glands, and uveal tract of the eye. The mediastinal and thoracic nodes are involved in some 75 per cent of cases, and are often visible in the x-ray film. I have seen a sarcoid lesion in the hypothalamus which caused diabetes insipidus, and two cases of myocardial sarcoidosis. To make matters more confusing, lesions may be confined to the skin or lymph nodes or bones or the eye. The bone lesions are practically limited to the phalanges of the fingers and toes. The disease lasts for months or years, with a tendency to fibrosis and healing. Healed lesions are represented by scars. In the lungs this scarring is of particular importance, because there can be little doubt that many cases which in the past have been considered as healed miliary tuberculosis are in reality examples of healed sarcoidosis. There may be quite generalized interstitial pulmonary fibrosis causing dyspnea and cyanosis due to failure of the right ventricle. Radiologically

the bones show a peculiar reticulated rarefaction in the early stages; later there are small punched-out areas. There is a remarkable alteration in the plasma proteins, consisting of an increase in the globulin fraction, usually with a pronounced elevation in the total plasma protein. In this respect the disease resembles multiple myeloma, kala-azar and lymphogranuloma venereum, in all of which elevation of the plasma globulin is a distinctive feature.

The lesions are rounded, circumscribed masses resembling miliary tubercles, the chief component of which is epithelioid cells, together with macrophages, giant cells, and occasional eosinophils. It may be difficult to decide between sarcoidosis and tuberculosis, particularly in a lymph node, but the peculiarly clean-cut, almost diagrammatic, character of the sarcoid lesions help the observer in his decision. The giant cells are larger than

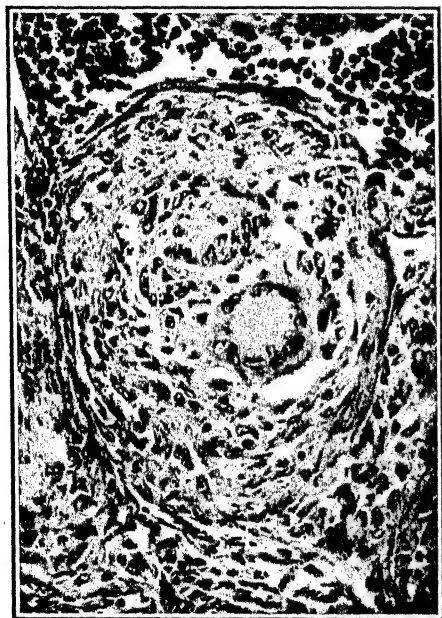


FIG. 64.—Sarcoidosis.  $\times 160$ .



FIG. 65.—Asteroid in giant cell in sarcoidosis.  $\times 1240$ .

those of tuberculosis and contain more nuclei (Fig. 64). Inclusion bodies, both "asteroids" and the spherical Schaumann bodies with calcified concentric laminations, may be a striking feature of the giant cells. Neither of these, however, is pathognomonic of sarcoidosis. The asteroid inclusions consist of clear areas containing a dark central body from which radiate delicate spinous processes giving an appearance of a starfish (Fig. 65). They may be derived from lipids which are no longer soluble in fat solvents or may represent protein deposits on former lipid crystals. Excellent illustrations of the various inclusions will be found in Engle's paper. There is a striking and characteristic absence of caseation, and there is generally no surrounding lymphocytic infiltration. Fibrosis increases with the age of the lesion. Silver stains show a delicate reticulum which is absent owing

to destruction in tuberculosis. In the later stages of the disease the lesions undergo a hyaline transformation. Teilum suggests that this is due to the precipitation of a homogeneous substance (?globulin) in the reticuloendothelial cells. This substance, which he refers to as paraamyloid because of its resemblance to amyloid, seems to be related to the hyperglobulinemia and may be a product of the plasma cells. The process may represent an antigen-antibody reaction. The difficulty is to name the antigen.

A fresh outlook on the natural history of the disease is suggested by Barrie and Bogoch. From an examination of a large amount of material they believe that granuloma formation is preceded by a diffuse mononuclear cell proliferation and infiltration in all the sites where granulomas are found, *i. e.*, the lymphatic and filter systems (nodes, spleen, marrow). A similar infiltration is found in the lungs, liver, heart, salivary glands, and central nervous system. These lesions are prominent only in early biopsies or when death has occurred early in the disease. It would appear that a foreign agent may be taken up by the mononuclear phagocytes, which react by proliferation and are changed into mononuclear cells, the granuloma representing a stabilization of the phagocytic process, the purpose being to isolate the foreign agent. The granuloma then disappears or may be followed by fibrosis. There may be widespread fibrosis of the lungs, which may explain some of the cases of so-called idiopathic pulmonary fibrosis.

The *etiology* of sarcoidosis is uncertain, or, if one prefers it, unknown. It may be an atypical manifestation of tuberculosis. The evidence in favor of this view is well summarized by Cameron and Dawson. Occasional cases are reported in which tubercle bacilli have been isolated from sarcoid lesions both by culture and animal inoculation. More probably it may be a chronic granuloma closely resembling tuberculosis histologically but caused by some undiscovered agent, possibly a virus. Pinkerton and Iverson have shown that subacute and chronic histoplasmosis gives clinical and pathological features identical with those of generalized sarcoidosis, the fungi when killed apparently liberating an antigen which stimulates the formation of noncaseating granulomas. The dead histoplasma, which may be invisible with hematoxylin and eosin, are shown up by the periodic acid-Schiff stain which colors the capsule. Such observations as these suggest that perhaps the wise view to adopt is that sarcoidosis is not an etiologic entity due to any one cause.

### TUBERCULOID LESIONS

Granulomatous lesions are not infrequently encountered which bear a resemblance to tuberculosis or sarcoidosis histologically, but which are not manifestations of these general disorders. Such lesions may be called tuberculoids. A sarcoid which is not associated with the generalized disease may also be regarded as a tuberculoid. A foreign body, a metal, a fungus, or an antigen liberated by disintegrating cells may excite histiocytic proliferation with the formation of epithelioid and giant cells, so that a non-caseating granuloma results.

The talc granuloma of the peritoneum due to the presence of crystals of magnesium silicate in the dusting powder of a surgeon's gloves is an example of a reaction to a foreign body. Beryllium granuloma is an example of a metal producing a similar reaction. Fungi such as *coccidioides immitis* and *histoplasma capsulatum* may cause lesions identical with those of sarcoidosis. Tuberculoid (sarcoid-like) lesions may occur in lymph nodes draining the seat of a primary carcinoma (Symmers). In such a case the granulomatous reaction may result from the presence of irritant products released as the result of necrosis or of the action of radiotherapeutic agents on the tumor. Sarcoid lesions may be seen in lymph nodes draining the lesions of Crohn's disease and even in the wall of the ileum. Giant cell granulomas in Riedel's struma of the thyroid which represent a reaction to liberated colloid may be mistaken for tuberculosis. Even a virus may excite a similar tissue response, as is seen in lymphogranuloma venereum. Many other examples of such tuberculoid reactions could be given.

From all this it becomes apparent that the diagnosis of tuberculosis on purely histological evidence is not as simple a matter as one might think, and this is even more true of sarcoidosis. McDonald and Weed point out that tubercle bacilli may be obtained by culture or animal inoculation from tissues on which a histological diagnosis of Hodgkin's disease and sarcoidosis has been made, and conversely that a biopsy diagnosis of tuberculosis may be reversed by the bacteriologist's subsequent report of brucellosis, histoplasmosis, or coccidioidomycosis.

As Engle points out, the sarcoid-like granulomas form a spectrum when considered with regard to inclusions. At one end there are the cases with giant cell inclusions of asteroid and lipid crystals; the granulomas are unexpected findings, they are unconnected with the cause of death, they occur in a limited number of organs, and they are associated in some cases with abnormalities of lipid metabolism. At the other end of the spectrum the inclusions are Schaumann bodies without lipids, the lesions are widely distributed, and there is no disturbance of lipid metabolism.

## LEPROSY

Leprosy, like tuberculosis and syphilis, is an infective granuloma, and a comparison of these three diseases makes a good exercise for the student of pathology. It is caused by *Bacillus lepræ*, an acid-fast bacillus closely resembling the tubercle bacillus. Unlike the tubercle bacillus, the bacillus of leprosy has not been cultured, nor have laboratory animals been infected successfully. The exact mode of infection is not known, but it is probably by direct contact. Ulcerated lesions of the nose and skin may discharge enormous numbers of bacilli. In spite of the popular opinion, the disease is only slightly contagious. Intimate and long-continued contact is necessary for infection to occur. Nurses and doctors in charge of leper colonies are very seldom infected if they take proper precautions. The incubation period is long and the exact time unknown.

The bacilli are distributed widely throughout the body, but the most important lesions are those of the skin and the nerves. Corresponding to these lesions two clinical types are recognized, the *nodular or tubercular form* and the *anesthetic form*. In the former nodules or masses are formed in the skin, particularly of the face,

hands, and feet; in the latter there are anesthetic patches on the skin. The two forms are frequently combined. A cellular granulation tissue is formed. This is composed mainly of large mononuclear cells known as *lepra cells*. These usually have a pale foamy appearance owing to a high lipid content. They may be crowded with acid-fast bacilli, the source of the lipid. Some of the cells attain a large size and may be called giant cells, but they are quite different from the multinucleated giant cells of tuberculosis. The new granulation tissue is diffuse, and does not show the grouping of the cells into follicles so characteristic of tuberculosis. Nor is there any caseation, but ulceration of the superficial lesions is common, so that there may be great destruction of the fingers, nose, ears, etc., with terrible disfigurement. Leprous lesions are found in the liver, spleen, and other organs.

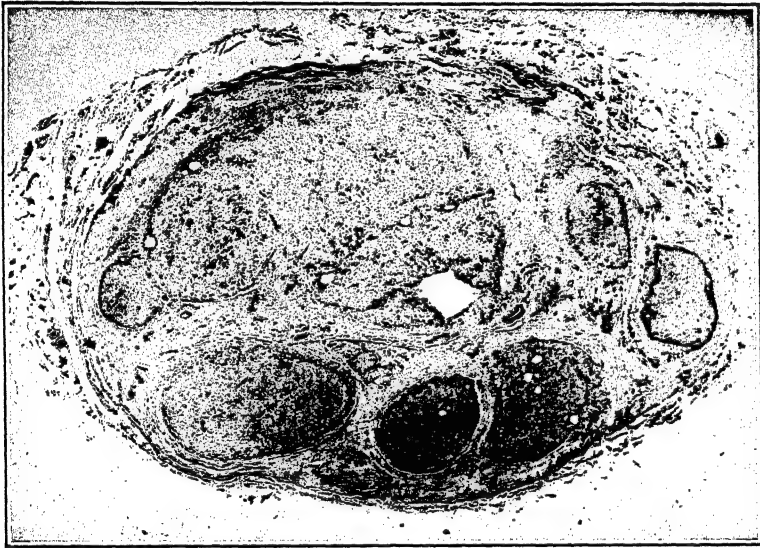


FIG. 66.—Nerve lesion in leprosy. Nerve bundles bound together by fibrous tissue.  $\times 18$ .

The lesions of the nerve trunks are peculiar to leprosy. They occur in the nodular as well as in the anesthetic form. There is a perineuritis, and the thickened nerves can be felt as cords under the skin of the arm and leg. The bacilli penetrate between the nerve bundles, and there is first a formation of loose granulation tissue and later fibrosis. (Fig. 66.) The nerve fibers are destroyed, so that anesthetic areas are produced, followed later by motor and trophic disorders. The destructive lesions already mentioned may be partly trophic, but in part they are due to loss of sensation with subsequent injury.

The clinical diagnosis is seldom difficult (nodular lesions and anesthetic patches), but in doubtful cases the acid-fast bacilli can be demonstrated in the discharge from the nose and the skin lesions, or a section of skin can be removed and stained for *lepra* bacilli. In active cases of the cutaneous type myriads of bacilli may be found in smears of serum made from a small incision in any part of the skin, even though it may appear quite normal. In the nerve lesions, on the other hand, bacilli can seldom be detected.

## SYPHILIS

Syphilis is a spirochetal infection in which the organisms enter through the skin or a mucous membrane, and become widely distributed throughout the body long before a local lesion is produced. Every organ may be infected, and nearly every disease may be simulated by syphilis. Of all diseases it is the most subtle. It is a master of disguise. There is no symptom which it cannot cause, no syndrome for which it may not be responsible. The incidence is said to be not less than 5 per cent of the population. At least 500,000 new cases occur every year in the United States. It is more common than measles, twice as common as tuberculosis and is responsible for 10 per cent of all cases of insanity. It is therefore essential to keep syphilis in mind in every differential diagnosis. The problems of the etiology and treatment of syphilis have engaged the attention of investigators for hundreds of years, but the fundamental contributions to our present knowledge were all crowded into the first decade of the twentieth century. In 1903 Metchnikoff and Roux succeeded in inoculating a chimpanzee with syphilis, in 1905 Schaudinn and Hoffman discovered the *Spirochaeta pallida*, in 1906 Wassermann published his complement-fixation test, and in 1910 Ehrlich introduced the arsenical treatment ("606") to the medical profession. This in turn has been replaced by penicillin. In the knowledge of no other disease have such extraordinary advances been made in so short a time. One of the most remarkable chapters in the history of syphilis is the story of how John Hunter inoculated himself on the glans and prepuce with the discharge from a venereal sore, and proceeded to observe and record with the detachment of the scientist the lesions as they appeared and disappeared over a period of three years. He experimented with various forms of mercurial treatment, but always stopped when there appeared to be danger of curing the disease. The story may be read in Long's Readings in Pathology.

Until recently syphilis was one of the most important diseases in the world, and the doctor had to know its multitudinous late manifestations as well as its early lesions. It has now fallen from its high estate on account of treatment with antibiotics, and the late manifestations are rapidly becoming a thing of the past. For this reason the following account will be greatly abbreviated from that of previous editions.

**Natural History of the Disease.**—In the vast majority of cases infection is acquired during sexual intercourse. The spirochetes may be present in recent lesions on the genital organs, or they may be transmitted in the semen many years after the original infection. There may be extragenital infection on the lips (kissing), mouth, tongue, fingers, or nipple (nursing an infected child). The spirochetes may penetrate an unbroken mucous membrane, but it is unlikely that they can enter the skin unless there is some crack or abrasion.

Syphilis is a general systemic infection in the course of which certain local lesions are produced which are sufficiently striking to attract clinical attention. Long before the first lesion (chancre) appears the spirochetes have infected the entire body. When an infected needle is passed through a rabbit's testicle and the testicle removed in forty-eight hours, in a week's

time the blood is so heavily infected with spirochetes that 0.5 cc. will transmit the disease.

When the spirochetes penetrate the surface they invade the perivascular lymph spaces, multiply exceedingly, and pour into the regional lymphatics and the blood stream. It is evident that no treatment of the local lesion, which only develops after general infection has occurred, can have any effect on that infection. The disease is divided clinically into three stages. These stages indicate that different sets of tissues are developing a hypersensitiveness which causes them to react to the irritant sufficiently violently to produce the symptoms of disease. The organs vary in the time they take to develop this hypersensitiveness, some are early, others late. The stages are separated by curious latent intervals. These stages and intervals have nothing to do with the spread of the infection, for that has already taken place.

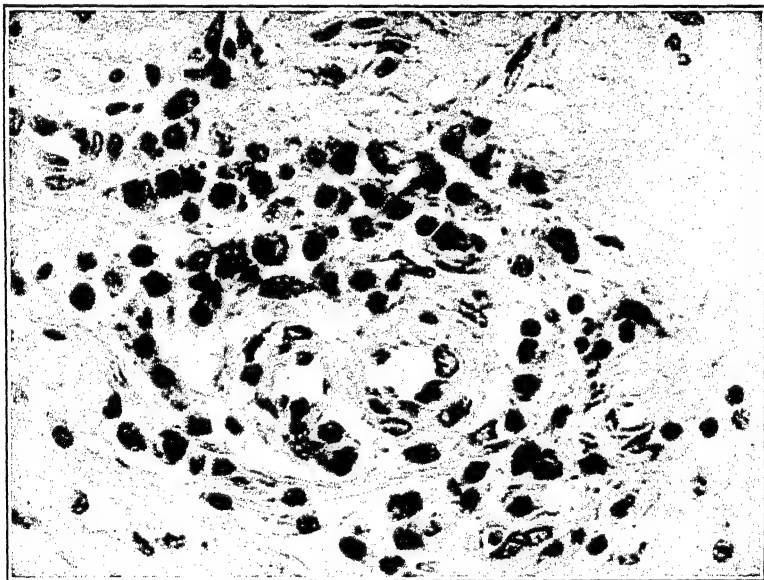


FIG. 67.—Syphilitic reaction. Lymphocytes and plasma cells collected around two small vessels with swollen endothelium.  $\times 500$ .

The spirochetes in the perivascular lymph spaces excite the syphilitic reaction. This consists of an accumulation of mononuclear cells, chiefly lymphocytes and plasma cells. (Fig. 67.) The latter is the characteristic cell of syphilis; in tuberculosis it is not at all prominent, but in non-specific inflammations it is sometimes present in large numbers. The new tissue is highly vascular in comparison with the avascular lesion of tuberculosis. Swelling of the endothelium lining the capillaries may cause narrowing of the lumen or obstruction. Fibroblasts are stimulated to proliferate, and when healing sets in there may be marked fibrosis. In late lesions (tertiary stage) necrosis is frequent (gumma formation) and is associated with the



presence of giant cells, but these are far less numerous than in tuberculosis.

As the result of the inflammatory reaction the spirochetes die out locally and healing occurs with replacement of the inflammatory cells by fibrous tissue. But unfortunately clinical healing does not correspond with cure,



FIG. 68.—Primary syphilitic lesion showing surface epithelium, marked vascularity swelling of vascular endothelium, and dense round-cell infiltration.  $\times 250$ .

and some of the spirochetes may survive. In the course of time the tissue immunity wears off, and then the spirochetes revive, multiply again, and cause a relapse. This sequence of events may take place in any part of the body, although it is least likely to occur in the primary lesion where the local reaction has been most violent. The testicles may appear normal

clinically, but virulent spirochetes may be discharged in the semen years after the Wassermann reaction has become negative and all gross signs of the disease have disappeared. It is evident that clinical healing is not synonymous with the cure of the disease.

**The Primary Lesion.**—The primary lesion appears at the site of inoculation. This is usually on the genitalia, but it may be extragenital (lip, fingers, etc.). The common genital sites are the penis in the male and the cervix in the female; the cervical chancre is highly infective on account of the moist character of its surroundings and it is easily overlooked owing to its hidden nature and freedom from pain and discharge. The primary lesion is generally single but may be multiple. It usually develops in from three to four weeks after infection, but this latent period may be as short as two or as long as six weeks. It first takes the form of a hard nodule, but the surface tends to become ulcerated and a "hard sore" or *chancre* is formed from the surface of which enormous numbers of spirochetes are discharged. These are most readily detected by means of the dark-field method. The chancre is the earliest clinical manifestation, but from the pathological standpoint the chancre is really a late affair, as we have already seen. The induration is due to dense cellular infiltration, but does not appear for the first few days. The floor of the ulcer is a dull red, but later it becomes glazed and coppery. It is characteristically insensitive. In the course of a few weeks healing occurs. Whether or not a scar is left depends on the amount of tissue destruction.



FIG. 69.—Spirochetes in tissue stained by the Levaditi method.  $\times 2500$ .

The microscopic appearance is that of all syphilitic lesions but lacking in "late" features; there is a dense accumulation of lymphocytes and plasma cells especially around the small vessels, and fibroblasts multiply and lay down collagen fibrils (Fig. 68). Destruction of tissue is seldom marked, but the surface epithelium is usually lost. If the section is stained by the Levaditi method an incredible number of spirochetes are brought to view (Fig. 69). The regional lymph nodes (inguinal, submental, etc.) are enlarged in the primary stage. These nodes are hard and shotty, but not painful or tender. They thus resemble the chancre in all respects. Microscopically the nodes usually merely show a diffuse hyperplasia. Puncture of the nodes will show spirochetes in the dark-field, and sections stained by the Levaditi method contain great numbers of spirochetes.

**The Secondary Lesions.**—After the appearance of the primary lesion there is a latent period during which apparently all is well. If the patient

has not received adequate treatment at the end of from two to three months after infection the tissues of ectodermal origin develop the power to react and lesions appear in the skin, mucous membranes, and central nervous system. These persist for a period of months and then disappear. There is no destruction of tissue (necrosis) at this stage, so that no scars are left, but there may be some coppery pigmentation.

*Secondary lymphadenitis* is one of the earliest changes. The nodes all over the body are enlarged in distinction to the regional involvement of the primary stage. The enlargement is never great, but it may persist for months or years. Swelling of the epitrochlear and posterior cervical nodes is specially characteristic.

**SKIN.**—The lesions of the skin are of great variety, but they are symmetrical in distribution (tertiary lesions are asymmetrical), they are polymorphous in type, *i. e.*, present several varieties of lesion at the same time, they possess a copper tinge, and their outline is that of the segment of a circle. Like other secondary lesions they do not destroy tissue. The lesions may be macular, papular or pustular. A *condyloma* is a large flat papule occurring in moist situations, *i. e.*, between the vulva, around the anus, etc. These are swarming with spirochetes and are highly infectious. There may be *mucous patches* of the mouth, pharynx, and vagina. These are flat superficial lesions which have been appropriately likened to the track left by a snail. They swarm with spirochetes and are highly infectious.

**The Tertiary Lesions.**—The subsidence of the secondary lesions is followed by another latent interval during which all is quiet. In a year or not for many years a third set of lesions appears. These are not symmetrical, they affect deep as well as superficial structures, and they show a tendency to necrosis and destruction. They are only slightly infective, for they contain only a few spirochetes. These are not easy to demonstrate in silver preparations.

Two main types of tertiary lesion may occur. The one is gross and localized (the gumma), the other is microscopic and diffuse. The *gumma* is a necrotic, localized, yellowish homogeneous mass of rubbery consistence composed of the usual mononuclear cells. It used to be so common that it had to be considered in the differential diagnosis of any mass of obscure character. Now it is hardly ever seen. In the center of the lesion necrosis and caseation occur with the formation of a peculiar gummy material, but there is not the same complete wiping out of structure as in tuberculous caseation: A few giant cells may be seen at the margin.

Gummata of the skin, mouth, tongue and nose may lead to extensive ulceration. The liver may show one or several masses (Fig. 70) which heal with fibrosis so that deep scars are formed, producing a peculiar lobed appearance known as *hepar lobatum*. In the testicle the gumma forms a hard mass which may be mistaken for a tumor; there is characteristic loss of testicular sensation on palpation. Gummata in the bones, the brain and other places used to be confused with tumors of these organs.

In the *diffuse lesions* the spirochetes are widely distributed and set up a diffuse chronic inflammatory reaction with lymphocytes and plasma cells, tissue destruction, but no caseation. The principal sites are the thoracic aorta and testicle. The most serious of all the late lesions are those of the

central nervous system which may come on many years after the original infection, especially when treatment has been inadequate. These may affect chiefly the meninges (syphilitic meningitis), the brain (general paresis of the insane), and the spinal cord (tabes dorsalis).

**Congenital Syphilis.**—Syphilis may be transmitted from the father or the mother, but in all cases the mother is infected, although often she shows no evidence of the disease. There are three possibilities. (1) The child may be born dead, usually showing well-marked evidence of syphilis. Syphilis is an important cause of still-birth. (2) The child may be born alive with external evidence of syphilis. (3) The child may appear healthy, but lesions develop later.

When the child is born dead the appearance is usually characteristic. There is no primary lesion, as infection takes place through the placenta. The child is usually premature and undersized. The skin may be macerated. If not, it usually shows bullæ. The spleen is enlarged, and often the liver. Syphilitic epiphysitis is one of the commonest and most diagnostic features. It is best seen at the knee by splitting open the lower end of the femur or upper end of the tibia. In place of the normal thin, regular, white epiphyseal line there is a broad irregular somewhat yellow line which is highly characteristic.

The chief *microscopic* change at this stage is an interstitial round-cell infiltration of many of the internal organs combined with a varying degree of fibrosis. In the liver this produces a fine form of intercellular cirrhosis. Levaditi preparations of the liver, heart, adrenals, etc., show enormous numbers of spirochetes. It is evident how infectious such a body must be, and great care is necessary in performing an autopsy.

If the child is born alive the skin may show the varied lesions already described in the acquired form. Common sites for the lesions are the buttocks, anus, angles of the mouth, and the palms of the hands and soles of the feet. Radiating scars are formed at the angles of the mouth which are very characteristic. The skin is often wrinkled, so that the child has a dried-up, wizened appearance. Enlargement of the spleen is very constant. The liver and other organs show the changes already described. The mucous membranes show the same lesions as in the acquired form. In the nose there is ulceration and destruction, so that the bridge of the nose may fall in giving the characteristic "saddle nose" of congenital syphilis. One of the most useful aids to diagnosis is roentgenographic evidence of epiphysitis and periostitis in the long bones.



FIG. 70.—Gumma of liver.

In the late type lesions develop over a period of years which stamp the patient as being a congenital syphilitic. The permanent teeth show the appearance known as "Hutchinson's teeth"; these are small, widely-spaced, peg-shaped (narrow at the apex), and the central incisors are notched. The molars are pitted and honey-combed. An interstitial keratitis develops at the time of puberty producing a ground-glass opacity in the cornea. Nerve deafness is common. The scars at the angles of the mouth known as rhagades have already been mentioned. Gummata develop in the bones, or a diffuse thickening affecting especially the tibia ("saber tibia"). There may be involvement of the central nervous system similar to that seen in the acquired form (juvenile paresis and juvenile tabes).

**BEJEL.**—This remarkable condition appears to be a non-venereal form of syphilis which is prevalent amongst the Bedouin Arabs. About 75 per cent of the Bedouins show evidence of infection, although there is no gonorrhea amongst them, and sexual promiscuity is unknown. It is a disease of the whole community, like measles, and is acquired in childhood, the infection being contracted from some other child in the acute stage, probably by means of drinking vessels. The earliest lesions are gray patches about the mouth, followed by a papular eruption on moist areas. In about a year, the lesions vanish, and the child appears healthy. They may never recur, but frequently gummata of bones, skin and pharynx appear many years later. The cardiovascular and nervous systems are not attacked. The Wassermann and Kahn reactions are positive.

**LYMPHOGRANULOMA VENEREUM.**—This venereal disease is commonly known as *lymphogranuloma inguinale*, but as that name is continually confused with granuloma inguinale, lymphogranuloma venereum is to be preferred. It is a contagious venereal disease caused by a filterable virus, which can be transferred to the monkey, rabbit and guinea-pig. The infection may, however, be non-venereal in children, doctors, nurses, and research workers. The virus is present in the primary lesion, regional lymph nodes, urethral and vaginal discharges, pelvic abscesses, blood stream, and spinal fluid. It has been demonstrated forty years after the original infection. The initial lesion is on the glans or vulva; it is small and indurated, heals quickly, and may never be noticed. Several weeks later the inguinal nodes become enlarged, indurated, matted together and painful, the overlying skin assumes a bluish-red color, fluctuation develops, and a purulent fluid is discharged, leaving a chronic ulcer of the skin with sinuses; these lesions may be extremely slow in healing. The microscopic picture is the same in the primary lesion and the lymph nodes. The basic lesion is a focal proliferation of large mononuclear cells which form aggregates. These cells accumulate around vessels, invade their walls, and finally obliterate their lumen (Sheldon and Heyman). This obliteration is not associated with endothelial proliferation or thrombosis. The result is the formation of small solid granulomatous nodules. Ischemic necrosis follows, with invasion by polymorphonuclears and the formation of stellate abscesses. After necrosis occurs intracytoplasmic inclusions (Gamma bodies) may be seen in the mononuclears. These represent phagocytosed cellular debris. When sterilized purulent fluid from one of the nodes is injected intracutaneously in a person suffering from the disease, it produces a marked allergic skin reaction. This is known as the intradermal test of Frei and Hoffmann, and the skin allergy on which it depends persists throughout life. When the virus is injected into the brain of monkeys or mice a meningo-encephalitis is produced, and brain emulsion makes a stable antigen for the Frei reaction which is preferable to using material from an infected person. Marked increase in the plasma protein is common. The disease is commoner in the negro but it often occurs in the white. Cole saw 52 cases in one year in Cleveland.

Rectal stricture is a common complication, and in the past has been incorrectly attributed to syphilis. Most authors agree that rectal lesions are much commoner in women, but Mathewson reports 74 cases in San Francisco, of whom 60 were men and only 14 women. The site of the primary lesion and not the sex determines the incidence of secondary lesions in the inguinal nodes or the rectal nodes. Owing to lymph drainage, infection of the glans and prepuce in the male and the clitoris and vulva of the female lead to inguinal lesions, whereas infection of the posterior urethra in the male and the vagina in the female are responsible for inflammatory lesions and subsequent stricture of the rectum. On these grounds rectal lesions might be expected to be more frequent in the female. The Frei-Hoffmann test is particularly useful in these cases of rectal stricture in the female with no external evidence of the disease. Lymphogranuloma venereum must not be confused with granuloma inguinale (see below). In the former the essential lesions are in the lymph nodes with secondary involvement of the skin, while the latter is primarily a disease of the skin. The presence of the Frei-Hoffmann test and the absence of Donovan bodies serve to characterize lymphogranuloma venereum.

### GRANULOMA INGUINALE

This is a chronic infective granulomatous condition practically confined to the negro and of common occurrence in the tropics and the southern part of the United States. It occurs in the anal and genital regions, commonly commencing on the penis and labia. The microscopic features are granulation tissue with a massive cellular infiltration, mainly plasma cells and remarkably few lymphocytes, together with a peculiar cell which Pund and Greenblatt have shown to be specific for this condition. The pathognomonic cell is a large mononuclear cell from 25 to 90 microns in diameter, presenting many sharply defined intracytoplasmic spaces which contain small deeply-staining round or rod-like bodies. The mode of transmission is not certain. Puncture of the granulomatous lesions shows the presence of numerous intracellular rod-like bodies in the mononuclear cells. These were first described by Donovan, and are best called Donovan bodies (to be distinguished from Leishman-Donovan bodies of kala-azar). The organism can now be cultivated on the yolk-sac of the developing chick embryo, and it has been named *Donovania granulomatis*. Occasionally the lesions are found in other parts of the body—face, mouth, back.

### THE MYCOSES

The mycoses are diseases produced by the higher fungi. The lesions are granulomatous in nature, and may therefore be ranked with those of tuberculosis, syphilis, and leprosy, but suppuration is common.

**Actinomycosis.**—This is the commonest of the mycoses in man, but the disease is much commoner in domestic animals (horses, cattle, pigs). It is caused by *Actinomyces bovis* or ray fungus, so-called because of the radiate arrangement of threads at the edge of the colonies. The fungus is a streptothrix which forms little yellow clumps in the tissue known as "sulphur granules." These clumps are composed of a felted mass of filaments with spores and club-shaped bodies at the periphery. The filaments are Gram-positive and the clubs Gram-negative. There are several types of actinomycetes, some aerobic, others anaerobic. The great majority of human and animal infections are due to anaerobes.

The method of infection is still uncertain. There is no evidence that it is conveyed directly from animals to man, but it is much commoner in

farmers and other country-dwellers. Ears of grain have been found embedded in the mouth lesions, and the usual view is that infection is carried by grain which has been chewed, but the *Actinomyces bovis* has never been found in grains or grasses in a state of Nature. The fungus probably becomes an inhabitant of the mouth or intestine in country-dwellers, and enters the tissues through some break in the surface, the root of a carious tooth, etc. Secondary invasion by pyogenic organisms is common, and the resulting suppuration may reduce the oxygen tension in the tissues and favor even more the growth of anaerobic actinomyces. When once penetration of the surface has occurred the wound heals promptly, and the pathological process works away from the mouth, intestine or rectum as the case may be.

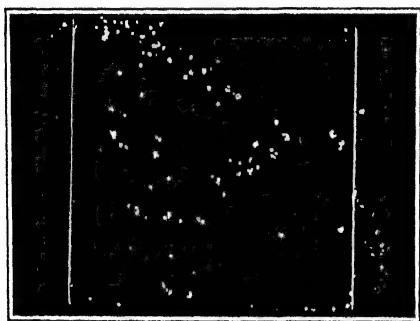


FIG. 71.—Sulphur granules, photographed on slide with black background.

A much rarer form of actinomycosis is that caused by *Nocardia asteroides*, which is aerobic in contrast to the anaerobic *Actinomyces bovis*. The lesions are far more widespread, involving a large number of organs as well as lymph nodes.

**SPREAD.**—The spread is different from that of tuberculosis and syphilis, for the lymph vessels and nodes are not involved, a valuable point in diagnosis. The infection starts in the subcutaneous or sub-mucous tissue and spreads by direct continuity. The lesion may

rupture into a blood vessel, and there may be blood spread to the liver, brain, and heart, but this is not common.

**LESIONS.**—The lesions occur in four chief sites: (1) head and neck (60 per cent), (2) ileocecal region and appendix (20 per cent), (3) lungs (15 per cent), and (4) the skin (5 per cent). A firm mass develops, usually under the lower jaw, followed by a brawny induration of the neck. After a time the mass breaks down and becomes riddled with abscesses and sinuses. These multiple sinuses perforating the skin are characteristic of actinomycosis. There is progressive destruction of connective tissue, muscle, and bone. The pus contains the tiny yellow *sulphur granules* from which the diagnosis can most readily be made. (Fig. 71.) These should be looked for whenever the abscess is opened, as they may disappear later. In the *abdominal form* a firm mass is formed in the cecum or appendix, which is very apt to be mistaken for carcinoma. Suppuration occurs and sinuses are formed in the abdominal wall. I have seen perianal lesions, probably from infection through the skin. In the *lungs* multiple abscesses are formed; these are surrounded by fibrous tissue, and the condition is easily mistaken for tuberculosis.

**Microscopic Appearance.**—The microscopic appearance is that of a granuloma with the addition of suppuration. (Fig. 73.) There are chronic

inflammatory cells, fibroblasts, and giant cells. If suppuration is marked the picture approaches that of acute inflammation. It is uncommon to find colonies of the fungus (Fig. 72); these are much more easily demonstrated in the discharge. It is evident that the histological appearance is not at all characteristic, and that not much need be expected from biopsy examination.

**ACTINOBACILLOSIS.**—This is an epidemic disease in cattle, very rarely affecting man. It closely resembles actinomycosis, but with the important difference that the lymph nodes are constantly involved. The pus is very viscous, and contains greyish-white granules. The center of the granules consists of a mass of minute Gram-negative bacilli, known as the actinobacillus, surrounded by radially disposed clubs. Thus the center of the granule is Gram-negative, whereas in actinomycosis it is Gram-positive.

**Blastomycosis.**—This is a chronic granuloma caused by a yeast-like fungus known as blastomyces. The organisms are spherical, two or three times the diameter of a red blood corpuscle, and show two characteristic features: (1) a clear double contour, and (2) budding-like yeast cells. They are demonstrated in the discharge from the lesions by adding a few drops of sodium hydroxide to the pus and examining unstained. The method of infection is unknown, but presumably it is through the skin by contagion. The disease occurs in two forms, cutaneous and systemic.

**Cutaneous Form.**—The cutaneous form is known as blastomycetic dermatitis. The lesions are commonest on the face, the back of the hand, and the front of the leg. At first they are papules, but they undergo suppuration and ulcerate. The disease spreads over the surface, so that a large area may be involved. The microscopic picture is similar to that of actinomycosis, *i. e.*, a granuloma (lymphocytes, mononuclears, giant cells) with suppuration added. At the edge of the ulcer there may be very marked epithelial hyperplasia which may closely simulate the appearance of epidermoid carcinoma. The spherical fungi are seen in sections of the tissue or in smears of the discharge (Fig. 74).

**Systemic Form.**—The systemic form is much less common. The lungs are most often involved, but any organ may be affected. Infection is spread by the blood stream. The pulmonary lesions are nodules and abscesses and are very liable to be mistaken for tuberculosis. The fungi are very numerous in the tissues in the systemic form. This form is nearly always fatal, but the cutaneous form is seldom fatal and may last for many



FIG. 72.—Colony of fungus in actinomycosis. Many mycelial threads can be seen in addition to the dense feltwork at the periphery.  $\times 275$ .



years. The various lesions are well illustrated in Baker's paper, and in that by Starrs and Klotz.

**Sporotrichosis.**—This is a chronic infection caused by the fungus *Sporotrichium*. In many respects it closely resembles blastomycosis, but the fungus is demonstrated by culture, not in smears. Like blastomycosis it is usually confined to the skin, but occasionally the internal organs are involved. The skin lesions are, as a rule, on the hand or forearm. They take the form of nodules which later break down and suppurate. The infection advances along the lymphatics, so that a line of nodules is formed along the arm, an appearance always suggestive of sporotrichosis. The microscopic picture is the same as in actinomycosis and blastomycosis, *i. e.*, a granuloma with suppuration. The disease is very chronic but is rarely fatal.

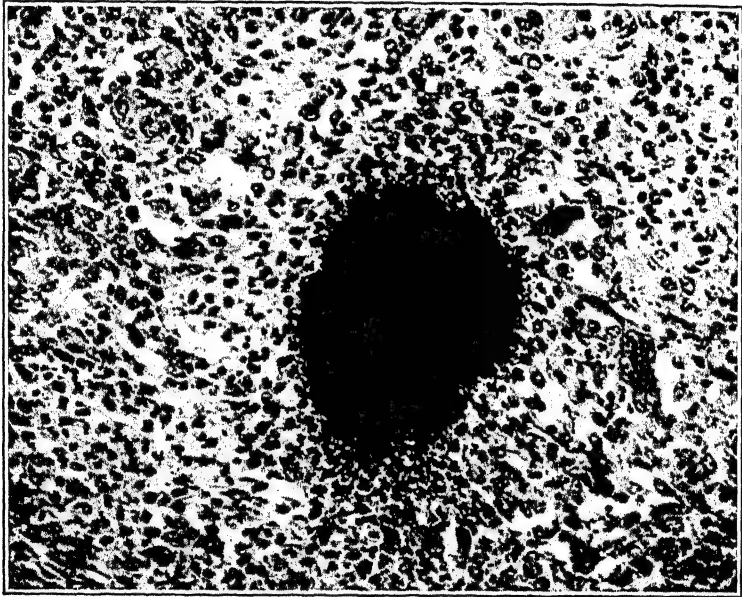


FIG. 73.—Actinomycosis showing suppuration immediately around central mass of ray fungus, and granulomatous lesion farther out.  $\times 200$ .

**Coccidioidomycosis.**—This uncommon disease was originally thought to be confined to the San Joaquin Valley, California, so that it came to be known as the "California disease." It is now known to be distributed all over the United States. It is an infective granuloma closely resembling tuberculosis, but caused by *Coccidioides immitis*, a yeast-like fungus. This is a spherical body with a double-contoured highly refractile capsule. It resembles the blastomyces, but can be differentiated by the fact that it multiplies by the formation of endospores, the blastomyces by budding. The coccidioides are much larger and may measure 50 microns. (Fig. 75.) Clinically the disease is easily mistaken for tuberculosis, syphilis and blastomycosis, and many cases of supposed tuberculosis are probably examples of this disease. Infection is due to the inhalation of dust containing the fungus. There is no passage of the infection from man to man. The morbidity is high, but the mortality relatively low. The infection has also been found in cattle. The disease can be reproduced in the guinea-pig, the characteristic lesion being a suppurative orchitis.

The *lesions* are usually in the lungs, bones and skin, but any organ may be involved. They are in the form of granulomatous masses and abscesses. They cannot be distinguished from those of tuberculosis with the naked eye, but it may be said that in the lungs there is less cavitation than is usual with tuberculosis and in the bones the lesions are more extensive. The microscopic appearance also resembles that of tuberculosis; tubercle formation, epithelioid cells and giant cells are common. (Fig. 76.) The pathognomonic feature is the presence of



FIG. 74.—Blastomycetes, one showing double contour.



FIG. 75.—Coccidioides in tissues.



FIG. 76.—Coccidioidal granuloma. Tubercle-like lesion, the right hand giant cell containing coccidioides.  $\times 200$ .

the double-contoured highly refractile coccidioides filled with spores. These are also found in pus from the lesions.

The work of Dickson has shed new light on the disease. He has shown that the condition begins as a mild infection of the respiratory tract often accompanied by erythema nodosum. The great majority recover promptly in the course of a few weeks, but in a few cases the mild attack is followed by the chronic granulomatous disease known as coccidioidal granuloma. Dickson suggests the term coccidioidomycosis to cover both forms.

**RHINOSCLEROMA.**—This is a disease of eastern Europe, and is seldom seen elsewhere except in emigrants from that part of the world. Although not a fungous disease, it is an infective granuloma. There is a hard swelling of the nose (*rhin*, nose; *sclera*, hard) which may spread to the pharynx and larynx. The microscopic diagnosis is made from the presence of peculiar large, round, clear cells filled with a



FIG. 77.—Mikulicz cell in rhinoscleroma.  $\times 1000$ .



FIG. 78.—Rhinosporidiosis.  $\times 152$ .

gelatinous material which may give the cytoplasm a foamy or reticulated appearance, and displace the nucleus to one side. These are known as Mikulicz cells. (Fig. 77.) They are often filled with bacilli resembling Friedländer's pneumobacillus. This bacillus is called *Bacillus rhinoscleromatis*, but it is not certain that the disease is caused by this organism.

**RHINOSPORIDIOSIS.**—This is a local inflammatory condition of the anterior nares, fairly common in India but extremely rare elsewhere, the only cases reported coming from the Argentine and the United States. It is rare in the female. The lesion takes the form of a polypoid growth in the nose composed of granulation tissue and presenting an extraordinary and characteristic microscopic picture, for the tissue is crowded with the huge parasitic cysts, each a single organism, which constitute the etiological agent (Fig. 78). This is a fungus known as *Rhinosporidium seeberi* (first described by Seeber), which commences its life cycle as a parasite measuring 8 microns, but grows by nuclear division until it reaches a size of 200 to

300 microns and contains over 4000 nuclei which form 16,000 spores. The mature parasite, now called a sporangium, presents a double-contoured chitinous envelope with a germinal pore, through which the spores are discharged. The mode of infection and transmission is unknown.

**HISTOPLASMOSIS.**—This is an uncommon, usually fatal fungus infection caused by a yeast, *Histoplasma capsulatum*. The organism is of about the same size and appearance as the Leishman-Donovan bodies of kala-azar, but it is a fungus, not a protozoön. In the body the fungus occurs as a yeast-like form; when grown outside the body it assumes a mycelial form. It has never been found occurring naturally outside the body. The disease was first described by Darling in 1906, and the titles of his two papers summarize many of the essential features: "A protozoön general infection producing pseudo-tubercles in the lungs and focal necrosis in the liver, spleen and lymph nodes," and "A fatal infectious disease resembling kala-azar." The lesions, which are widespread anatomically, are granulomatous in type, sometimes tubercle-like, with areas of necrosis. The reticulo-endothelial cells, which are greatly swollen, are crowded with parasites (Fig. 91), and the mononuclear cells of the peripheral blood may show a similar appearance. The parasite is beautifully demonstrated by the McManus P.A.S. stain (periodic acid-Schiff reaction). A diagnosis may be made from biopsy of a lymph node, and the fungus can be cultured from the blood. Fever, anemia, leucopenia and *splenomegaly* are prominent features of the clinical picture. An intradermal skin reaction with histoplasmin, an antigen derived from *Histoplasma capsulatum*, has been developed. Through epidemiological studies with this test it now appears that many of the cases of pulmonary calcification with non-tuberculin reactions may be due to mild or subclinical histoplasmosis. The reliability of the reaction, however, has not yet been fully determined.

**GLANDERS.**—Glanders is one of the infective granulomata, and in its chronic form may readily be mistaken for tuberculosis, syphilis, or actinomycosis. It is one of the diseases transmitted from animals to man. As it affects horses, the human disease is seen in grooms, veterinary surgeons, etc.

The disease is caused by *Bacillus mallei*, a slender Gram-negative rod resembling the tubercle bacillus. The Strauss reaction is used for diagnosis. The suspected material is injected in the peritoneal cavity of a male guinea-pig, and within twenty-four hours an acute inflammation develops in the tunica vaginalis. The fluid from the tunica is implanted on potato, and a yellow honey-like culture is obtained.

Infection occurs from the nasal discharge of a diseased horse, and enters the body through a crack in the skin or the mucous membrane of the nose. After an incubation period varying from a few days to two or three weeks the primary lesion appears. At first this is a papule, later becoming a pustule. The lesions are spreading and destructive, with the formation of large irregular ulcers. The infection spreads along the lymphatics causing nodular swellings, which in the horse are known as *farcy buds*. The lymph nodes are swollen, and there is destruction of connective tissue and muscle. The *microscopic* appearance is that of an infective granuloma but without caseation. Giant cells are rare. Unless the bacilli can be demonstrated, a correct diagnosis may be extremely difficult. The infection may last for months or years; in the end it usually proves fatal.

An *acute* form occurs both in man and the horse. It is a septicemic condition, with the formation of pyemic abscesses in the lungs, liver, kidneys, etc.

## ANTHRAX

Anthrax is also one of the diseases transmitted from animals to man. It is very prevalent in European animals, especially cattle and sheep, but is

much less common in North America so that human infection is comparatively rare in this country. Infection is nearly always conveyed through the skin, rarely by inhaling infected material (wool-sorter's disease) or by swallowing it. The latter is the common method by which animals are infected, so that in them the lesions are usually intestinal. In man the lesions are nearly always in the skin; pulmonary and intestinal lesions are very rare. Infection is conveyed from the wool and hides of diseased animals, so that butchers, tanners, wool-sorters, etc., are the chief sufferers. The bristles of a new shaving brush may carry the infection. It is said that biting flies may convey infection from animals to man, but this seems open to doubt.

The anthrax bacillus is a large, square-ended, Gram-positive bacillus, the most important characteristic of which is the power of forming very resistant spores outside the body. For this reason infected wool, hides, shaving brushes, etc., may remain a source of danger for years. As the spores are not formed inside the body it is of the greatest importance when disposing of the body of an animal which has died of the disease that no blood should be shed, otherwise the spores will remain in the ground for years and serve to infect other animals.

The *skin lesion* is the *malignant pustule*. It commences as a pimple on an exposed part of the skin (face, hands). This soon develops into a vesicle (not a pustule) containing clear serous or blood-stained fluid swarming with anthrax bacilli. The diagnosis is readily made by staining a smear of this fluid. When the vesicle bursts a black eschar is formed, around which a fresh row of vesicles develops; further out there is a brawny induration. The microscopic picture is one of acute inflammation. The rare *pulmonary* and *intestinal lesions* are similar in nature, *i. e.*, they show an acute hemorrhagic inflammation.

At any stage the bacilli may enter the blood stream causing an anthrax septicemia with infection of all the organs. This is constantly seen in highly susceptible animals such as the mouse and guinea-pig. The post-mortem findings are those of a hemorrhagic septicemia, with enlargement of the spleen, etc. From what has already been said, it will be obvious that extreme care must be taken at the autopsy to prevent the formation of spores.

### ANAEROBIC GAS-FORMING INFECTIONS

Infection of a wound by a member of the group of anaerobic gas-forming bacilli results in gas gangrene. There are three members of this group: (1) *Bacillus welchii* or *Bacillus aerogenes capsulatus*; (2) *Vibrio septique*, probably identical with the bacillus of malignant edema; (3) *Bacillus oedematiens*. These are all saccharolytic, not attacking proteins if carbohydrates are available, and they grow best in tissues containing an abundance of carbohydrate, *i. e.*, muscle and liver. To these three may be added *Bacillus sporogenes*, which has strong proteolytic powers and soon produces putrefaction with its characteristic smell. It is not pathogenic nor gas-producing, but it breaks up the proteins. *Bacillus welchii* is the commonest invader and the chief gas producer. As well as producing gas gangrene it

is the cause of postmortem gas formation. Except when grown in special media it does not form spores, but in tissue fluids it has a well-marked capsule. (Fig. 79.) The other organisms readily form spores.

These bacteria are putrefactive. They are unable to gain a footing in living tissue until it has been devitalized. They are ordinarily saprophytes. Thus *B. welchii* was found in 80 per cent of wounds in the First World War, yet less than 10 per cent of these developed gas gangrene. Trauma and other organisms fail to activate it, but soil and dead muscle act as a spark which lights the fire. As the organisms feed on muscle sugar, it follows that early excision of dead muscle is the best prophylactic. Gas gangrene is a disease of muscle, which is at first a dull red and then becomes green or black. Bubbles of foul-smelling gas and blood-stained fluid can be pressed up and down the length of the muscle. The bacilli spread up and down the muscle in the interstitial tissue, and the muscle fibers are separated from their sheaths by toxic fluid, as a result of which they are killed and are then invaded by the putrefactive bacteria. (Fig. 80.)



FIG. 79.—*Bacillus welchii*, showing capsules.  $\times 1000$ .

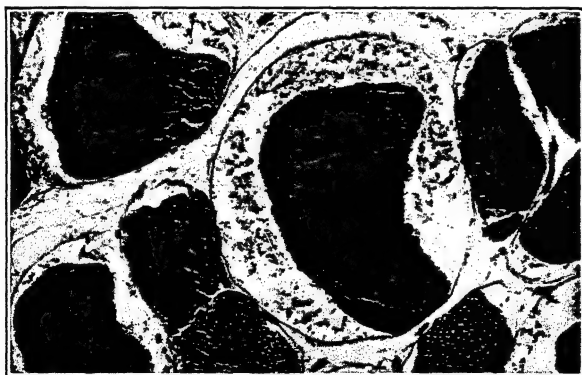


FIG. 80.—Gas gangrene. A muscle fiber separated from its sheath and from its blood supply by gas and fluid.  $\times 250$ .

## TETANUS

Tetanus is a disease caused by wound infection with an anaerobic bacillus, *Bacillus tetani*, but it differs entirely from the group of anaerobic infections just described, for there are no local symptoms. The bacillus develops a terminal spore, which gives it the familiar drumstick appearance.

The organisms can be seen in the pus from infected wounds. The disease is an infection of septic wounds, not merely a wound infection. Its growth is favored by the presence of aerobic bacteria, so that it is never found in pure culture in a wound. The bacillus is a normal inhabitant of the intestine of the horse and other animals, and is therefore found in ground which has been manured. Wounds contaminated with garden soil, the dirt of streets, etc., are therefore always liable to infection by tetanus. Civilians with wounds of this character and all wounded soldiers must be protected by a prophylactic injection of antitetanic serum.

The *incubation period* varies greatly, averaging from ten days to a fortnight. In the case of face wounds it may be only three or four days. If the spores are surrounded by scar tissue they may remain quiescent for months. A subsequent operation, as for removal of a foreign body, may activate the spores, so that a second injection of serum should be given before such an operation.

The bacilli remain in the wound and produce a toxin which acts on the central nervous system. The tetanus toxin is one of the most powerful toxins known. For long it has been believed that the toxin was absorbed from the motor nerve endings and passed along the axis cylinders to reach the spinal cord. In 1934 Abel attacked this view and brought forward experimental evidence suggesting that the toxin is absorbed by the lymphatics and distributed to the central nervous system by the blood stream, where it acts on the motor nerve cells. Abel also suggested that the toxin may act directly on striated muscle, thus explaining the phenomenon of "local tetanus," which may develop in the wounded part long before the general symptoms manifest themselves. Abel's theory is supported by the observation of Barnes and Trueta in 1941 that tetanus toxin is not absorbed from an immobilized limb in an experimental animal, for lymph flow from a part ceases when it is immobilized. When the toxin reaches the cord and brainstem it becomes so firmly anchored to the motor nerve cells that it cannot be dislodged.

The symptoms are the result of an extreme hypersensitiveness of the motor nervous system produced by the action of the toxin on the motor nerve cells. As the result of this the most trivial sensory stimuli produce a series of terrible clonic and tonic spasms, and the patient dies exhausted by his convulsions or asphyxiated by tonic spasm of the respiratory muscles. As the condition is purely toxic and not inflammatory, no characteristic lesions are found at autopsy.

*Postoperative tetanus* is fortunately rare. It is usually due to catgut infection with the spores of tetanus. When the catgut is absorbed in the wound the spores are set free and develop into bacilli. Not every case is due to the catgut. The dressings, dusting powder, etc., may be infected. Finally it must be remembered that the patient may be an intestinal carrier of tetanus bacilli which may reach the tissues through an operation wound involving the bowel.

### BUBONIC PLAGUE

The disease is caused by *Bacillus pestis*, an extremely virulent organism. It gains entrance to the body through the skin, sometimes through the

lungs by inhalation of infected droplets of sputum especially in the pneumonic form. It penetrates the skin usually by the bite of a flea which conveys the infection from the rat to man, but it may enter through cuts and abrasions. The disease may occur in endemic or epidemic forms. A human epidemic is accompanied or preceded by a rat epidemic. When a rat dies the infected fleas leave it and go in search of a new victim. The problem of plague control is the problem of the deadly triangle of the rat, the flea, and the man.

**LESION.**—The lesions are glandular and general. The inguinal and axillary lymph nodes become much enlarged, suppurate, and form buboes. This is a regional lymph node infection, the result of inoculation through the skin. The nodes at first show ordinary inflammatory hyperplasia, but abscess formation and hemorrhage follow. The bacilli invade the blood stream and are found in enormous numbers in the internal organs, where they produce necrosis, abscesses, and toxic changes. The patient dies of an overwhelming septicemia before there is time for very marked lesions to develop.

**Pneumonic Form.**—In bubonic plague some changes are always found in the lung such as small patches of consolidation and great engorgement with large numbers of bacilli in the alveoli. Sometimes the epidemic takes a pneumonic form, in which infection is spread by tiny droplets of sputum. There are no buboes, and the patient is overwhelmed by one of the most deadly and rapidly fatal of all infections. There is not time for any extensive pneumonic consolidation, so that here also the changes are a patchy consolidation with intense congestion and alveoli crowded with plague bacilli. The rest of the body shows evidence of an overwhelming septicemia.

**HEMORRHAGIC SEPTICEMIA.**—This is a group of infections rather than a single disease, caused by organisms closely related to the plague bacillus (*Pasteurella* group) and affecting many of the lower animals. Members of the hemorrhagic septicemia group are chicken cholera (*Bacillus avisepticus*), swine plague (*Bacillus suisepiticus*), and mouse typhus (*Bacillus typhi murium*). Some of these hemorrhagic septicemia infections may occasionally involve man. It will be realized that plague itself is a hemorrhagic septicemia.

**Whooping Cough.**—Whooping cough or pertussis is an acute infectious disease of the respiratory tract, as a result of which there are spasmodic attacks of coughing with a prolonged inspiration known as a "whoop." The disease consists of a catarrhal stage of one or two weeks' duration marked by a hard dry cough (this is the infectious period), and a paroxysmal stage of four to eight weeks' duration marked by severe paroxysms of coughing and whooping, and by attacks of vomiting. Common complications are bronchopneumonia, atelectasis, emphysema and convulsions. One attack of the disease confers immunity for life.

The *etiological agent* appears to be *Bacillus pertussis* of Bordet and Gengou, a minute Gram-negative hemophilic bacillus, which is found in great masses entangled in the cilia of the bronchial mucosa. Rich and his associates have shown that in chimpanzees the oral inoculation of pure cultures of Bordet-Gengou bacilli resulted in a condition similar in all respects to whooping cough, and characterized by coryza followed by a



protracted paroxysmal cough, associated with lymphocytosis and a positive complement fixation toward the Bordet-Gengou bacillus.

The lesions are tracheitis, bronchitis, and the characteristic interstitial bronchopneumonia with infiltration of the walls of the bronchi and bronchioles by lymphocytes, plasma cells and large mononuclears. Masses of *Bacillus pertussis* cause matting of the cilia, but fail to penetrate below the surface. It is possible that they produce a toxin which acts on the central nervous system and especially on the nuclei of the vagus and recurrent laryngeal nerves, accounting for the paroxysmal coughing and the attacks of vomiting.

## TULAREMIA

Tularemia is another plague-like disease which affects both animals and man and is spread from the former to the latter. In animals it has the virulence and septicemic qualities of plague, but in man the infection is milder and recovery is the rule. In spite of this greater resistance man is extraordinarily susceptible to the infection. Although related to plague, the symptoms in man may closely simulate typhoid fever, and the lesions may as closely resemble those of tuberculosis. The disease is a new one, or rather a newly-recognized one. It was first observed as an acute epidemic infection among ground squirrels in Tulare County, California, and the *Bacterium tularense* was discovered to be the cause. Later it was found that the infection could be conveyed to man. At first it was thought that tularemia was a disease peculiar to the United States. Its problems have been worked out by American bacteriologists, and by Francis in particular. It is now known that it is world-wide in distribution. It is transmitted to men from a rodent, not from another man. The great reservoir of the disease is the ground squirrel and the jack-rabbit, but many other rodents are now known to harbor the infection. The domestic rabbit does not suffer from the disease. Infection is carried in three ways: (1) by biting flies, particularly the deer-fly, *Chrysops discalis*; (2) by ticks; (3) by contact with the skins or internal organs of infected rabbits. It therefore occurs in farmers, hunters, market men, butchers, housewives, and cooks. The microorganisms enter through cracks in the skin or through the eye. Laboratory workers handling and performing autopsies on infected animals are extremely liable to infection, even though alive to the danger.

Two types of the disease may be recognized in man, the glandular and the typhoid.

*Glandular Type.*—This resembles a mild form of bubonic plague, except that a local lesion develops at the site of inoculation. After an incubation period of a few days there is a sudden onset with pains, prostration and fever. The regional lymph nodes draining the site of infection become enlarged, inflamed, and tender. If the portal of infection is the eye the preauricular, submaxillary, and cervical glands are involved. Not until twenty-four hours later does a papule appear at the site of infection. Both the primary lesion and the lymph nodes undergo necrosis, suppuration, and ulceration. The bacteria have not been demonstrated in the tissues, but a bacteremia occurs early, and a positive blood culture can be obtained

during the first week. By the end of the second week agglutinins appear and reach their height in the third week. After that they decline, but persist in small amounts for several years. Cross-agglutination occurs with *Brucella melitensis*, so that the disease may be confused with undulant fever. Recovery is the rule, but convalescence may take some months.

*Typhoid Type*.—Here there is no obvious primary lesion and therefore no glandular involvement. The portal of entry is unknown, but it is probably the unbroken skin, for the bacilli can penetrate the skin of the guinea-pig and set up a septicemia. The typhoid type is usually due to laboratory infection.

**LESIONS.**—In man the lesions may be of two types, acute and chronic. The *acute* lesions are characterized by focal necrosis and suppuration (Fig. 81). These changes are seen in the primary lesions and the regional lymph nodes, and to a lesser extent in many of the internal organs (spleen, liver, lung). The *chronic* lesions resemble those of tuberculosis for which they are easily mistaken. They are focal in type with central necrosis, epithelioid cells and giant cells.

**DIAGNOSIS.**—The disease is apt to be mistaken for typhoid fever (when no primary lesion is present), for undulant fever (because of cross-agglutination), and for tuberculosis (a mistake made by the pathologist on account of the glandular lesions). When the physician thinks of tularemia on account of the primary lesion, the regional lymph node enlargement, and the history of having dressed a wild rabbit or of being bitten by a tick or fly, he can confirm his diagnosis in two ways: (1) agglutination of *Bacterium tularensis* by the blood serum in the second week, and (2) isolation of *Bacterium tularensis* from guinea-pigs inoculated with material taken from the primary lesion or enlarged glands or with the patient's blood. The guinea-pig will die in a week and show enlarged caseous lymph nodes and a spleen studded with tiny foci of necrosis. Smears and cultures taken from the patient are useless.

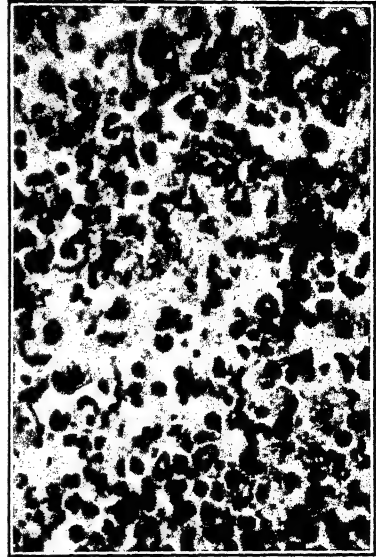


FIG. 81.—Tularemia.  $\times 490$ .

**CAT SCRATCH DISEASE.**—This disease, although only recognized in 1951, appears to be of wide distribution. It is probably caused by a virus, but as it resembles and is readily confused with tularemia it is considered here.

There is always a history of an association with cats, but, in spite of the name, there is not necessarily evidence of a scratch or bite. There may be an initial skin lesion, or there may be enlargement of regional lymph nodes without any evident

primary lesion. The lymphadenitis is often suppurative, but the pus is sterile. The microscopic picture is one of reticuloendothelial hyperplasia followed by necrosis. The chief elements are polymorphonuclear leucocytes, epithelioid cells, and occasionally giant cells. The infection pursues a benign course. An intradermal skin reaction similar to the Frei test for lymphogranuloma venereum is of diagnostic value, using an antigen made from the pus.

### UNDULANT FEVER: BRUCELLOSIS

This disease, like tularemia, is an infection of animals which may be conveyed to man. Like tularemia it is in some respects a new disease, in other respects it is not. It is caused by the *Brucella* group of microorganisms named after Sir David Bruce, who first isolated them many years ago in Malta fever. The organism is a very small cocco-bacillus which has been called both a coccus (*Micrococcus melitensis*) and a bacillus (*Bacillus abortus*). It has long been known as the cause of Malta fever, an infectious disease of goats in the Mediterranean countries and conveyed to man in goat's milk. It has also been known for some time as *Bacillus abortus*, the cause of contagious abortion in cattle. The infection is extraordinarily common in cattle. Thus it has been shown that 90 per cent of the herds in Connecticut are infected. It should be noted that though the cows have a tendency to abort, and pass large quantities of the bacilli in the milk, they show no evidence of disease. The goats also suffer no inconvenience from *melitensis* infection. It was not until 1918 that an intimate relationship was demonstrated by Evans to exist between *Brucella melitensis* of Malta fever and *Brucella abortus* of contagious abortion. The two are closely related but not identical. The most important step was the last, when in 1924 Keefer showed that *Brucella abortus* was infective for man. The various forms are best included under the name of undulant fever, of which there is a *melitensis* type and an *abortus* type. The *abortus* infection may come from swine (porcine form) or cows (bovine form). The *abortus* infection is not so pathogenic for man as the *melitensis* form. Most of the persons who drink infected cow's milk show no evidence of the disease, though they may have agglutinins in the blood. Thus the morbidity for the human subject is low.

Infection is acquired *via* the alimentary tract, usually by drinking unpasteurized cow's milk, so that most human cases in temperate countries are examples of *abortus* infection. In view of the fact that this is a milk infection it is curious that the disease is rare in children. Laboratory infections may be acquired through cracks in the skin, the scratch of an infected needle, etc. Contact infection may also occur in workers in packing houses, farmers, veterinarians, and others who come in contact with infected material. The method by which infection passes from one animal to another is not certainly known. Undulant fever used to be regarded as a rarity. In 1926 only 46 cases were reported in the United States, but in 1929 over 1300 cases were reported. It is undoubtedly very much commoner than is usually thought. It should enter into the differential diagnosis of every long-continued fever when such conditions as typhoid, tuberculosis and subacute bacterial endocarditis are being ruled out. The

mortality is low, less than 2 per cent. *Brucella* infection may not give rise to typical undulant fever but merely to persistent malaise and indisposition with some irregular fever. In endemic areas a certain proportion of the population suffers from a latent infection, so that the blood gives a positive reaction to the agglutination test. Women with latent infection may show a tendency to abortion.

The disease begins insidiously with an evening rise of temperature, and the patient may be ill for some time without knowing that he has any fever. Persistent weakness, muscle pains, arthritis, and marked perspiration with a peculiar sweet sickly odor to the sweat are some of the common features of a disease which may easily pass unrecognized. Orchitis is an occasional symptom. The fever may come in waves, hence the name undulant fever, though this is not common, and the infection may last for months and even years. Three months is an average duration. There is a remarkable absence of positive physical signs, owing to the general rather than the local character of the infection. The spleen is palpable in more than a third of the cases. The lymph nodes may be enlarged. A blood culture may be obtained at the height of the fever, but it is often negative, and has to be kept at least a week before any growth is apparent. The culture should be kept for five weeks before being discarded as negative. The organisms are often excreted in the urine, and a culture may be obtained from a catheterized specimen. Agglutination is the most reliable means of diagnosis. Agglutination with a titer of 1 in 100 or over in the presence of fever and the other clinical symptoms indicates active infection. A titer of 1 in 100 in the absence of clinical symptoms indicates latent infection. A titer of 1 in 80 and under in the absence of clinical symptoms indicates a past infection. Occasionally active cases fail to give agglutination, but this is uncommon. A source of confusion is a cross-agglutination with *Bacterium tularensis* which sometimes occurs.

**LESIONS.**—Very few studies of the autopsy findings in undulant fever have been recorded owing to the low mortality of the disease. The spleen is enlarged, averaging 500 grams, and there is a general swelling of the mesenteric lymph nodes. Inflammatory masses may involve the soft tissues, the bones or the viscera. These show a nonspecific chronic inflammatory cell reaction with granulomatous formation, necrosis, and epithelioid and giant cells. Sections of excised lymph nodes are apt to be mistaken for tuberculosis by the pathologist, but cultures from the tissues are positive for *brucella*. Parsons and his associates state that chronic brucellosis of the glandular type as seen in North Carolina may present a picture similar to that of Hodgkin's disease; *B. melitensis* in pure culture was grown from the lymph nodes.

## SPIROCHETAL FEVERS

**SPIROCHÆTOSIS ICTEROHÆMORRHAGICA. WEIL'S DISEASE.**—This is a form of infectious or epidemic jaundice caused by the *Spirochæta icterohæmorrhagicæ*. It is therefore considered in the discussion on jaundice in Chapter 21, page 519.

**RELAPSING FEVER.**—This is a disease of tropical countries, though some cases have been reported in the United States. It is characterized by a peculiarly recur-

ring type of fever. The febrile attacks last a few days and are separated by short periods during which the patient feels quite well. The disease is caused by several closely related species of spirochetes, of which *Spirochaeta obermeieri* was the first described and is the best known. During the febrile attacks the spirochetes are present in the blood in great numbers, but during the afebrile intervals they vanish. The infection is conveyed by lice and ticks. These do not inject the organisms directly into the blood, but when the body of the louse is crushed on the surface by scratching, the spirochetes are liberated and penetrate through the skin abrasions. The mortality is not high. The postmortem lesions are those of septicemia, notably enlargement of the spleen, cloudy swelling of the internal organs, and hemorrhages in the serous and mucous membranes.

## BARTONELLA INFECTIONS

**OROYA FEVER.**—This is a disease occurring in Peru characterized by intermittent fever and a severe rapidly progressive anemia, ending fatally in a large number of cases. The red blood corpuscles contain minute rod-like motile organisms first described by Barton in 1909 and known as *Bartonella bacilliformis*. A large proportion of the erythrocytes may be affected. It is now known that the fatal cases are those which are complicated by paratyphoid B infection. In cases in which paratyphoid infection has not occurred the prognosis is good, no matter how great the destruction of red blood cells.



FIG. 82. —*Bartonella muris*. (McCluskie and Niven.)

Certain strains of rats may become infected with another type of *Bartonella*, *Bartonella muris*. The infection remains latent, no organisms are found in the red blood cells, but a few days after splenectomy severe and fatal anemia rapidly develops, due to invasion of the red blood cells by the *Bartonella* (Fig. 82), just as in Oroya fever. The latency

appears to be due to the inhibitory action of the reticulo-endothelial elements in the spleen.

## VIRUS DISEASES

Viruses may attack plants (mosaic diseases, etc.), possibly bacteria (? bacteriophage), animals (foot and mouth disease, distemper, vaccinia, hog cholera, etc.), and birds (psittacosis). They are responsible for a great number of diseases in man, which may conveniently be placed in the following seven groups: (1) *Skin* (dermotropic): smallpox, chickenpox, molluscum contagiosum, measles, lymphogranuloma venereum. (2) *Nervous system* (neurotropic): poliomyelitis, rabies, herpes (zoster and simplex), postvaccinal encephalitis, probably encephalitis lethargica and encephalomyelitis. (3) *Nasopharyngeal mucosa* (catarrhal): coryza, influenza, measles. (4) *Glands* (glandular): mumps, infectious mononucleosis. (5) *Proliferative*: verrucae, molluscum contagiosum, Rous sarcoma, Shope papilloma. (6) *Systemic*: psittacosis. (7) *Insect vector*: yellow fever, dengue.

It is a common mistake to think that viruses are merely very minute bacteria, or that they are of a nebulous and almost theoretical character. They differ from bacteria in the following particulars. (1) *Size*. The viruses are called ultramicroscopic, but this is not strictly correct, for the largest can be seen in the form of so-called elementary bodies, and the electron microscope has brought many members of the group within the range of vision. They range in size from 5 to 30  $\mu$ . (2)

*Filterability.* They can all pass through the pores of the finest unglazed porcelain filter, but this is not all-important as the name filterable virus would suggest, for many minute bacteria such as *Bacillus influenzae*, *Brucella abortus*, and most spirochetes are filter-passers. (3) *Cultural characters.* Bacteria can live on lifeless material such as gelatin and agar, but viruses can only grow in media which contain living cells. They can be grown *in vitro* (tissue culture) or *in vivo* (chorioallantoic membrane of developing chick). They are said to be cytotropic, because they appear to penetrate and live inside the cells whether in the body or in a culture medium. They do not multiply in the body fluids, and thus differ from bacteria. (4) *Specific inclusion bodies* are very characteristic of true virus diseases. We can only recognize the presence of viruses by the effects they produce—"by their fruits ye shall know them"—and the most easily recognized effect is the cellular inclusion. They are not present in all, for, as Cowdry remarks, nuclear inclusions are the fingerprints of a special and limited group of viruses, and viruses, like human beings, may act without leaving fingerprints. It is doubtful if all intracytoplasmic inclusions are necessarily an indication of virus infection. The inclusions may be cytoplasmic or intranuclear; sometimes both forms are present. In some diseases, such as fowl-pox, vaccinia and psittacosis, cytoplasmic inclusions consist of aggregates of virus particles, which when dispersed are known as *elementary bodies*. In other diseases, such as rabies and yellow fever, the status of the inclusion body is uncertain. Some "inclusions," particularly intranuclear ones, may represent products of degeneration. Inclusions represent the intracellular pathology of the virus diseases. The best-known examples are the Guarneri bodies of smallpox (Fig. 83), the Negri bodies of rabies, the Lipschütz bodies of herpes, and the molluscum bodies of molluscum contagiosum. They are also found in yellow fever, poliomyelitis, and psittacosis. Excellent illustrations of the various inclusion bodies are to be found in Cowdry's article in Rivers' book on *Filterable Viruses*. The inclusion bodies were known long before filterable viruses were dreamt of, for the molluscum bodies were described in 1841. (5) *Selective action.* To a much greater degree than in the case of bacteria viruses attack one particular tissue. Thus the virus of smallpox attacks the epithelial cells of the skin, the virus of poliomyelitis the motor anterior horn cells of the spinal cord, the virus of louping-ill (sheep) the Purkinje cells of the cerebellum. (6) *Resistance to germicides.* Although readily destroyed by heat, viruses can resist the action of substances (glycerin, etc.) which quickly kill bacteria, so that they can be isolated from material contaminated by bacteria by this means.



FIG. 83.—Inclusion bodies. The Guarneri bodies of smallpox. (Kindness of Dr. J. Craigie.)

The nature of viruses is a matter of uncertainty. There is even doubt on so fundamental a question as to whether or not they are living, whether they are obligate parasites which require living cells for multiplication or merely the products of cellular perversion which are reproducible in series. Some may belong to one group, some to the other. Rivers sums up the matter in his Harvey Lecture: "Some viruses may be minute living organisms representing the midgets of the microbic world, others may be primitive forces of life unfamiliar to us, still others may be inanimate transmissible incitants of disease." The viruses may be situated

near the line that separates inanimate, transmissible incitants from minute living organisms. The transition from one side of the line to the other may be so gradual that no great difference in the types of disease caused by agents near the line is perceptible. Stanley has obtained a crystalline protein from tobacco plants infected with tobacco-mosaic disease which has all the properties of a virus. It is still infective after ten crystallizations, and can reproduce the disease in a dilution of 1 in 1,000,000,000. Such a substance cannot be regarded as living in the ordinary sense of the word. The tobacco-mosaic virus may be considered as an autocatalytic protein which requires the presence of living cells for multiplication. Laidlaw points out that parasites lose the power of making substances which are essential to them if these can be found ready-made in the cells of the host. This laziness may be such that the power of independent metabolic activity is lost. The parasite would then be living a borrowed life, and would consist merely of nucleo-protein possessing the power of reproduction, but inanimate outside the cell. Some viruses have achieved a partial and others a total degree of social security. The latter are completely dependent on the state, even to the extent of requiring permission for reproduction.

*Virus immunity* differs in many respects from immunity to bacterial infection. One attack of a virus disease usually confers a life-long immunity. This is true of measles, mumps, chickenpox, smallpox, herpes zoster, poliomyelitis, yellow fever, and dog distemper. The immunity seems to be due to a cellular rather than a humoral change, for although the blood of persons who have recovered from poliomyelitis contains immune bodies, these are not proportionate to the degree of active immunity produced. The immunity may also be due to a continued sojourn of the virus within the body long after recovery has taken place. Thus in the infectious anemia of horses it was found that the blood was infective as long as fourteen years after an attack. Most plants that are infected with virus diseases retain the virus as long as they live. When they recover they are immune and cannot be reinfected. An anti-virus serum can be produced, but the protective substance in the serum does not appear to combine with the virus. Both the protective substance and the virus are fixed by the tissue. If fixation of the virus precedes that of the protective substance, infection of the cell is not prevented, but if fixation of the protective substance precedes that of the virus, infection is prevented. When the virus becomes fixed to the cell it is protected by the latter, and the neutralizing antiserum is unable to affect it. The immune bodies in the serum seem to act directly on the virus without the intervention of complement or leucocytes which are so essential in bacterial immunity.

The *lesions* produced by viruses are varied. There may be: (1) cellular changes, (2) inflammation, or (3) no detectable lesion. The *cellular change* is the primary one. It may take the form of hyperplasia, degeneration or lysis. The hyperplasia is marked in such lesions as verruca vulgaris (warts), molluscum contagiosum, fowlpox, the Rous sarcoma of chickens, the Shope papilloma, and the virus-produced adenocarcinoma of the frog's kidney described by Lucké. The virus evidently stimulates the cell to reproduce. Cell division is usually amitotic, but numerous mitoses may also be seen. (What relation, if any, has this to the problem of cancer?) Degeneration of the cells attacked is seen in smallpox, herpes, poliomyelitis, rabies, etc. Lysis is best seen in the phenomenon of bacteriophagy. *Inflammatory changes* occur in many virus diseases, but they are secondary rather than primary. The characteristic cell is the mononuclear or lymphocyte, no matter how acute the disease, but there may be many polymorphonuclears, as in poliomyelitis. The central nervous system is a common site of virus diseases in man, and here the inflammatory lesions usually take the form of perivascular collections of mononuclear cells.

With this survey of the general characteristics of virus diseases, some of the examples in man will now be described.

**Smallpox.**—Smallpox or *variola* is an acute infectious fever characterized by the formation of “pocks” or pustules in the skin. Headache and persistent pain in the back are characteristic symptoms. After an incubation period of ten to twelve days the skin lesions appear and slowly develop. At first they are papules, in the course of a few days these become vesicles, and the vesicles are converted into pustules, over which scabs are formed. Healing occurs under the scabs or crusts, but when these are cast off a scar may be left. The depth of the scar depends on whether or not the destructive process has reached the cutis vera. The disease is extraordinarily contagious, the infection being conveyed by the discharge from the lesions and by the crusts. This may happen from personal contact, from contact with clothing or possessions of the patient, or by air transmission, the virus being carried on particles of dust from the scabs. Before the introduction of vaccination the disease used to be as common as measles. It was seen mostly in children, because a previous attack bestowed on adults a permanent immunity. Macaulay with characteristic rhetoric speaking of 17th Century England paints this picture: “The small pox was always present, filling the churchyards with corpses, tormenting with constant fears all whom it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of the betrothed maiden objects of horror to the lover.”

*Alastrim* is a form of smallpox met with principally in South America. It differs from smallpox in having a very low mortality, but is probably a variant of that disease due to the same cause.

**Etiology.**—Smallpox is a good example of a disease caused by a cytotropic filterable virus. The infective agent is a filter-passer, characteristic inclusion bodies are found in the local lesions, and there is a topical reproduction of the virus. The virus can be grown in artificial culture with pieces of growing skin, multiplication being shown by the result of subsequent inoculation, which is the only method of proving that a filterable virus is still active. The inclusion bodies were first described by Guarnieri, and are known as *Guarnieri bodies* (Fig. 83). They are present in the cytoplasm of the epithelial cells of the skin lesions and are easily produced by applying a small quantity of virus to a scratch in the cornea. They may be merely a degeneration product of cytoplasm, but it appears more probable that they represent some multiplying form of the virus, a colony of the minute granules which are seen in the discharge from the lesions and in vaccine lymph, and which seem to constitute the actual infective agent.

**Lesions.**—Only some of the lesions of smallpox are specific, *i. e.*, are due to the virus itself. The others are due to the secondary streptococcal infection which seems to occur in every case. The streptococci are responsible for the pustular lesions, and usually for the death of the patient. The specific lesions are the papules and vesicles of the skin. The virus is epitheliotropic and multiplies in the epidermis. There is a peculiar degeneration of the epithelial cells which become swollen (ballooning) and undergo liquefaction. The change is more marked at the periphery of the lesion, so that the edges are raised, giving the center a sunken or umbilicated appearance. There is a fluid exudate in the vesicular stage, but this is clear



and almost free of cells. When suppuration occurs it is crowded with pus cells. In the vesicular stage there are abundant plasma cells in the tissues, but in the pustular stage these are replaced by polymorphonuclear leucocytes. The Guarneri bodies have already been described. The mucous membranes of the mouth and nose show the same lesions as the skin. In the internal organs there are lesions of focal necrosis (liver, kidney, heart) due to the secondary infection. Inflammatory necrotic nodules in the testicle are common. Death is often due to bronchopneumonia.

**Rabies.**—Rabies or hydrophobia is a disease affecting animals (carnivora, *e. g.*, dog, wolf) and man. The infection is transmitted to man by the bites of rabid animals, the infective agent being excreted in the saliva. The incubation period is fortunately remarkably long, usually over two months, and in rare cases as long as a year. This gives time for preventive treatment. The length of the incubation period depends on the position of the bite, being very much shorter in bites of the face and head than in bites of the leg, for a reason that will be apparent shortly. The principal symptoms are cerebral irritation, pharyngeal spasm especially at the sight of water so that the patient is unable to drink, and generalized convulsions. The disease is invariably fatal unless preventive treatment is employed.

*Etiology.*—Rabies, like smallpox, is a good example of a cytotropic virus disease. It is caused by a filter-passing agent which is neurotropic, so that the true lesion is in the nerve cells of the brain. The disease can be produced by inoculating an emulsion of the brain of a rabid animal into the subcutaneous tissue of another animal. It may, if wished, first be passed through a Berkefeld filter. As the symptoms are cerebral it is evident that the virus must pass from the site of inoculation to the brain. Like other viruses it does not travel by the blood stream, but passes along the peripheral nerves, probably along the axis cylinders, as Goodpasture has shown to be true of the virus of herpes simplex. It is for this reason that the incubation period is long for bites on the foot, short for bites on the head; it is all a question of how far the virus has to travel. Once the virus reaches the central nervous system it is rapidly disseminated throughout the brain and spinal cord.

*Lesions.*—There are no naked eye changes apart from congestion of the gray matter of the brain and cord. Microscopically there is cell degeneration, phagocytosis of the degenerating cells, and collars of inflammatory cells (lymphocytes and plasma cells) around the small bloodvessels. The pathognomonic feature is the presence of Negri bodies. These are inclusion bodies varying much in size found in the cytoplasm of the ganglion cells in the hippocampus major as well as in the cells of the medulla, cerebellum, etc. They are acidophilic bodies with a blue center. When a dog suspected of rabies has bitten a patient, the dog's brain must be examined for Negri bodies. The most rapid method is to take a cover-glass impression of the cut surface of the hippocampus major, but a more certain method is to stain sections. The nature of the Negri bodies is still a matter of dispute, for those best qualified to judge are divided in opinion as to whether they represent aggregations of the virus or merely degeneration products of cellular origin.

*Preventive Inoculation.*—It is rather strange that the modern treatment of rabies is that introduced by Pasteur who had never heard of filterable viruses or Negri bodies. Pasteur found that the spinal cord of rabbits infected with the disease was rich in the virus, as shown by the results of animal inoculation. He also found that he could lower the virulence of the virus by the simple expedient of hanging up the cord and allowing it to dry. By drying a series of cords for varying lengths of time he obtained a series of viruses of varying virulence. Treatment is of no avail once the symptoms have manifested themselves, but Pasteur availed himself of the very long incubation period which is so striking a feature of the disease. He found that if inoculation with attenuated virus was commenced within five days of receiving the bite it was successful in nearly 100 per cent of the cases, that is to say there was complete prevention. This is surely an extraordinary *tour de force* for the earliest days of modern bacteriology.

**Yellow Fever.**—Yellow fever is an acute infection with high fever, acute nephritis, hemorrhages in the skin and from the stomach and bowels, and jaundice. It occurs in certain endemic centers in Central and South America and in West Africa which in the past have served as starting-points of epidemics. The American centers have been almost completely controlled, but that is far from being true of West Africa, where both Stokes and Noguchi died of yellow fever while investigating the disease. The mortality is above 60 per cent, but if recovery takes place a permanent immunity is established. The virus is transmitted from one person to another by a mosquito, *Stegomyia fasciata* (*Aedes ægypti*). Twelve days must elapse before the mosquito becomes infective for another person. The story of the Reed Commission which worked out the method of transmission, and of General Gorgas who waged war on the stegomyia and cleansed Havana and Panama of yellow fever after they had been infested for centuries, is one of the romances of medicine.

A notable advance is the discovery of an animal which can be infected experimentally. The Reed Commission had to use two of their own num-bers as experimental animals to prove that infection was conveyed by the mosquito, and Lazear died as the result of the experiment. Stokes showed before his death that the monkey can be infected, and all the recent work has been done on *Macacus rhesus*. It is now possible to demonstrate the presence of immune bodies in the blood of the majority of the inhabitants of some West African villages, as their blood will protect a monkey against inoculation with infected material. Moreover a vaccine has been prepared from the liver of monkeys which have recently died of yellow fever. This vaccine will completely protect a monkey from a dose of 1 gram of infected liver, although a dose of 0.0001 gram is fatal for non-immunized animals, a truly remarkable degree of immunity.

*Lesions.*—These serve to explain very completely the clinical symptoms. The virus attacks the capillaries, the liver, and the kidneys, so that there are hemorrhages, jaundice, and marked urinary disturbances. There is hemorrhage into the stomach, thus giving the "black vomit" which is so characteristic of the later stages. The intestine may be full of blood. There are hemorrhages in the myocardium, endocardium and epicardium. The most characteristic of all the lesions is the "Councilman lesion" of the

liver. This is a non-inflammatory hyaline necrosis affecting many liver cells and forming a dense acidophilic mass in the cytoplasm. As the condition advances areas of necrosis are produced and the bile passages are ruptured with escape of the bile into the blood, but it is the early discrete lesion which is really characteristic. Intranuclear acidophilic inclusion bodies have been described in the liver cells in both the human and the experimental disease. (Hoffmann.) There is an extensive necrosis of the renal epithelium, so that the convoluted tubules are blocked with necrotic cells; the marked albuminuria, abundant casts, and final anuria are natural sequels, and they are among the worst prognostic signs. The spleen is of normal size, but shows a striking loss of lymphocytes. Congestion and hemorrhages in the lungs are common.

**Poliomyelitis.**—Poliomyelitis is an acute infection of the grey matter of the spinal cord and brain, and will be described in connection with Diseases of the Nervous System. As it happens to be a virus disease, some of the bacteriological features will be considered here.

The virus is an ultra-microscopic filter-passer, and is markedly neurotropic. It becomes associated with the motor cells of the central nervous system whether it is injected into the brain, painted on the naso-pharyngeal mucous membrane, or inoculated into a peripheral nerve. Like the virus of rabies, it appears to pass along the axis cylinders of the nerve until it reaches the central nervous system, where it becomes widely disseminated. The symptoms may suggest a localized infection, but the nervous lesions are always widely spread. The very important practical question of route of infection and method of spread of the disease are considered in Chapter 31, page 835.

Intranuclear inclusion bodies have been described by Hurst in degenerating cells in the early stage, but not when the cell has become necrotic. As in other virus diseases immunity is life-long. The blood contains immune bodies many years after the acute attack, and these have been used for the treatment of early cases.

**Herpes.**—There are two different forms of herpes, herpes simplex (febrilis, labialis, cornealis, genitalis) and herpes zoster. *Herpes zoster* follows the distribution of the spinal nerves, is accompanied by changes in the spinal fluid, and the attack is followed by permanent immunity. *Herpes simplex* is recurrent, does not follow the line of nerve distribution, and is not accompanied by changes in the spinal fluid. Both are probably virus diseases, the site of attack being the sensory nerve ganglia.

It is a remarkable fact that when the virus of herpes simplex, so harmless in man, is inoculated into the cornea of a rabbit, a fatal encephalitis is produced. Goodpasture has shown that the path of absorption is along the axis cylinders of the nerve supplying the part, whether it is sensory, motor, or sympathetic. The histological criterion for the action of the virus is the presence of Lipschütz bodies, which are intranuclear inclusions found both in the epithelial cells of the primary lesion (skin or cornea), and in the nerve cells in the brain or cord from which nerve fibers pass to the part affected. In both instances they are a proof of the direct action of the virus on the cells.

**Mumps.**—Mumps or epidemic parotitis is caused by a virus which can be demonstrated in the saliva. The disease can be reproduced in monkeys by injection of a filtrate of saliva from human cases into Stenson's duct. The lesions produced by the virus are epithelial necrosis and round cell infiltration of the interstitial tissue. Inflammation of the testis (orchitis) occurs occasionally, and rare complications are acute pancreatitis and meningo-encephalitis.

**Measles.**—Measles because of its extreme contagiousness is one of the commonest diseases in the world. It is probable that the causal agent is an ultra-microscopic virus. The life-long immunity conferred by one attack supports this view. A second attack is extremely rare. Contagion is due to direct exposure to a case of the disease. The experimental injection of infected blood into human volunteers and monkeys has been successful in producing the disease.

The immunity following an attack of measles is associated with the presence of immune bodies in the serum, and these can be used as a means of treatment and prevention. Measles is an outstanding example of a virus disease, which can be controlled by immune serum therapy. The immune serum may prevent or modify an attack.

The chief *symptoms* are fever, the characteristic rash, and evidence of an acute catarrhal infection of the upper respiratory tract and eyes. The commonest complication is bronchopneumonia.

In the *skin* the chief change is a round-cell infiltration about the blood-vessels, hair follicles, and sweat glands. In the deeper layers of the epidermis there are areas of colloid degeneration of the epithelial cells passing into coagulation necrosis. These areas are surrounded by fibrin and leucocytes, and are probably due to the direct action of the virus on the epithelium.

The *mucous membrane* of the mouth and upper respiratory tract shows catarrhal inflammation. In the mouth the epithelium is thickened and in places shows foci of fatty degeneration, giving rise to the white dot which forms the center of the Koplik spot, the pathognomonic sign of measles.

The *lungs* of fatal cases nearly always show bronchopneumonia. This should be regarded as a complication rather than as an essential lesion. If the patient recovers from the bronchopneumonia he may develop an acute form of pulmonary tuberculosis due to the lowered resistance produced by the virus.

The *lymph nodes* and *spleen* may be swollen, but never to any great extent. A peculiar giant-cell formation may occur in lymphoid tissue. This has been observed in the tonsils (Warthin) and in the appendix in the prodromal stage. Monkeys injected with blood from measles patients show giant cells in the lymph nodes (Gordon and Knighton). The spleen is seldom palpable. The *liver* often shows areas of focal necrosis. The *brain* may be the seat of a meningo-encephalitis, a lesion which will be described in connection with that disease. The *blood* shows a characteristic leucopenia, due to a diminution in the number of polymorphonuclear leucocytes. This forms a striking contrast to the leucocytosis of scarlet fever.

**Influenza.**—Influenza is the most puzzling of all the infectious diseases. It is usually the mildest of infections, lightly referred to as “a touch of the flu.” At long intervals it suddenly assumes a virulent form, and like “a blast from the stars” great epidemics and pandemics sweep across the world killing millions of people. At such times, as in the 1918-1919 pandemic, it seems that “the Angel of Death is abroad in the land; you can almost hear the beating of his wings.” During that pandemic 500,000,000 were attacked and 15,000,000 were killed, more than were killed amongst all the combatants in World War I. Are these two diseases the same although of different intensity? It is hard to say, because we have no criterion by

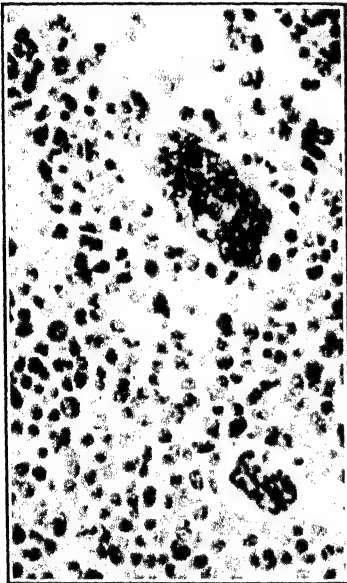


FIG. 84.—Tonsil in measles.  
× 360.

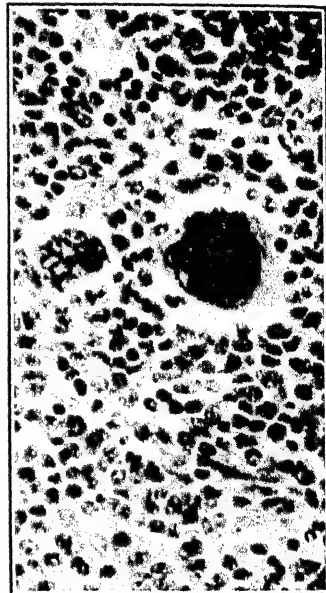


FIG. 85.—Appendix in measles.  
× 360.

which influenza can be recognized with certainty apart from its epidemic character. There is no infallible clinical symptom, no certain laboratory test, no pathognomonic autopsy lesions.

**ETIOLOGY.**—At the end of the great pandemic of 1889-1892 Pfeiffer found a minute Gram-negative hemophilic bacillus in the sputum and bronchial passages of influenzal patients, and concluded that this must be the cause of the disease, so that it became known as *Bacillus influenzae*. It has now been established that epidemic influenza is caused by a virus, or rather by at least two viruses, A and B, of which A is by far the commoner; B has only been found in small isolated outbreaks. The two viruses are perfectly distinct, as shown by neutralization tests with immune serum. None of the ordinary laboratory animals are susceptible to direct inoculation from man, but in 1933 Smith, Andrewes and Laidlaw showed that ferrets are

susceptible and also swine. After passage through the ferret white mice can be infected by instillation into the nostrils. Ferret infection is contagious whereas mouse infection is not. The explanation of the difference is simple; the ferret sneezes and the mouse does not. Pneumonia only occurs after either anesthesia or after repeated passage through ferrets. The solid lung is bacteriologically sterile, but rich in virus. The virus responsible for the great 1918 pandemic can no longer be isolated from man. It has vanished. It used to be believed that the virus passed into swine, causing the swine influenza which appeared in 1918, and that it survives in swine though dying out in man. Unfortunately this pretty theory has now to be abandoned. The cause of endemic influenza, commonly called grippe, has not yet been determined. It is apparently not due to either the A or B virus of epidemic influenza.

The part which other organisms may play in association with a virus is well illustrated by Shope's work on swine influenza. This disease can be produced experimentally in pigs by means of a filterable virus acting in conjunction with *Hemophilus influenzae suis*, a small hemophilic organism which is present in the natural disease, but is quite unable to induce the disease by itself when inoculated intranasally. The virus alone was unable to produce the typical disease, but did cause an exceedingly mild infection which was contagious. The combination of the comparatively innocent virus and a culture of *H. suis* produced severe and typical lesions, so that it appeared as if the virus conferred powers of invasion on *H. suis*. Some such coordinated mechanism may be at work in human influenza.

*Lesions.*—The lesions of fatal cases of influenza will be described in connection with diseases of the respiratory system. It may be said here that in all cases the essential lesion seems to be an acute inflammation of the upper respiratory tract, commencing in the nasopharynx, affecting the sphenoidal and other air sinuses, and passing down to cause a tracheo-bronchitis. Patches of interstitial pneumonia with mononuclear collections in the bronchial walls similar to those already described in measles form a characteristic feature. The influenzal pneumonia with great hemorrhagic edema in the pulmonary alveoli which is so frequently seen at autopsy is probably due to secondary invaders.

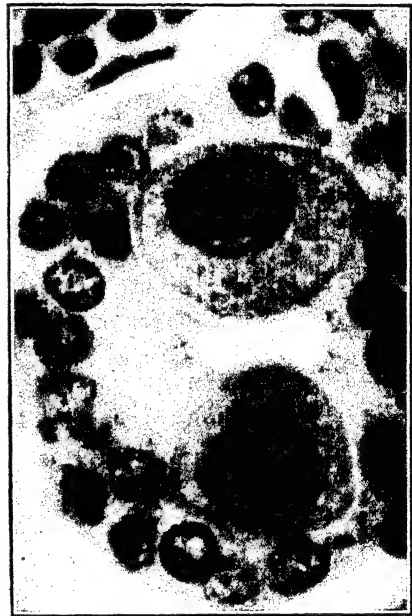


FIG. 86.—Salivary gland inclusion disease.  
(Kindness of Dr. W. L. Donohue.)

**INCLUSION DISEASE.** This condition is also known as cytomegalic inclusion disease and generalized salivary gland virus infection. The occurrence of inclusions in the salivary glands of the newborn, infants and young children has long been recognized. The inclusions may be intranuclear or cytoplasmic. The former may occur alone, the latter never in the absence of the former. The intranuclear body is a large dense mass which is acidophilic or may be purplish with hematoxylin and eosin (Fig. 86). The cytoplasmic bodies are small and basophilic. The infection appears to be primary in the salivary glands, and the lesions are identical with those of salivary gland virus disease of rodents. The human disease, however, is not transmissible to animals, nor does growth take place on eggs or tissue culture, so that the evidence in favor of a virus is merely by analogy. In rodents the infection is confined to the salivary glands, but in the child it may become generalized and cause death. A great variety of organs may be affected, but the liver, kidney, pancreas (islets of Langerhans) and lung (interstitial pneumonia) deserve special mention. Excellent illustrations of the inclusions will be found in the papers by Smith and Vellios, and by Wyatt, Saxton and Pinkerton.

**PSITTACOSIS.**—This is another disease of animals occasionally transmitted to man. It is a disease of South American parrots and parakeets (*psittakos*, parrot), often known as parrot fever, and when a pandemic occurs among the birds, small epidemics are certain to appear in the countries to which the parrots are exported. Canaries and finches in contact with parrots may acquire the infection. Man to man infection may occur, but is not common. The last notable epidemic occurred in 1929-1930 in many parts of Europe and America, but even in epidemic periods the disease is really rare. It is extremely infective for laboratory workers investigating the disease, even though they have not come in actual contact with diseased parrots. The virus is present in the nasal discharge and feces of infected birds, contaminates the air in the vicinity of the cages, and is inhaled by persons in the vicinity.

The onset is sudden with fever, intense headache, gastro-intestinal disturbance, and a clinical picture often mistaken for typhoid fever. The physical signs, on the other hand, are those of an atypical pneumonia. There is consolidation and cough, but no sputum, pleurisy or leucocytosis. The presence of a parrot in the history is necessary for a positive diagnosis. The mortality in the English cases was 20 per cent. There is a reliable complement fixation test, but it is also positive with the serum in lymphogranuloma venereum; the Frei reaction is also positive in psittacosis.

For long it was thought that a bacillus of the paratyphoid group, first described by Nocard and known as Nocard's bacillus or *Bacillus psittacosis*, was the causal agent. It was shown in 1930, however, that the agent was a filterable virus.

**Lesions.**—The chief lesions are in the lungs. There is a patchy pneumonia, but with very little fibrin in the exudate and no fibrinous pleurisy. The really characteristic lesion, however, is a remarkable swelling of the epithelium lining the alveoli and a proliferation of the cells as indicated by numerous mitotic figures. The proliferated cells may become desquamated and form characteristic clumps and plugs in the alveoli. Apart from this the human lesions are not characteristic, for they are very varied, due probably to secondary infections. In inoculated mice foci of necrosis are found in the spleen and liver. The bronchioles are filled with an exudate which blocks the lumen and causes areas of collapse to be formed. Rickettsia-like inclusions have been described in the endothelial cells of the lung, liver and spleen in parrots which have died of the disease. Other lesions in the body are a moderate degree of enlargement of the spleen and congestion of the internal organs.

**EPIDEMIC HEMORRHAGIC FEVER.**—This disease has been endemic in the Far East for many years and has been reported by Russian and Japanese observers in Manchuria and Siberia. It has been brought to the attention of Western medicine

by the occurrence of many cases amongst the United Nations' forces in the war in Korea (Mayer; Hullinghorst and Steer). It is believed to be a virus or rickettsial disease, the infective agent being carried by small rodents such as the field mouse and mole, with a mite as the insect vector, but none of this has so far been proved. The portal of entry is not known. The agent is extremely virulent, must multiply rapidly, and appears to produce a diffusible capillary toxin which gives rise to widespread hemorrhages. The condition is different from any other known hemorrhagic disease. The chief clinical features are oliguria, anuria, uremia, shock-like episodes, severe hemorrhage, and pulmonary edema. The hemorrhage appears to be in the nature of a diapedesis of red cells resulting from vasoparalysis rather than an extravasation due to rupture of vessels. There is a striking absence of jaundice, perhaps related to the fact that the red cells in the tissues do not undergo hemolysis. The course is fulminating, over half the fatal cases dying in eight days or less, some within two days. Death seems to be due to shock and renal failure.

The principal lesions are: (1) widespread capillary hemorrhage but without apparent capillary damage or thrombosis; (2) a peculiar type of coagulation necrosis suggestive of infarction, but without vascular occlusion; (3) a cellular infiltrate consisting mainly of mononuclear macrophages seen principally in the myocardium, pancreas, spleen and liver. The cellular infiltrate is not related to the necrosis nor the hemorrhage. The hemorrhage is most severe in the gastrointestinal tract and the kidneys. The necrosis is best seen in the kidneys, pituitary and adrenals.

The *kidneys* present a dramatic picture to which the Russians have given the name of renal apoplexy. The organs are enlarged, the average weight being over 500 grams. Perirenal hemorrhage is frequent. The cortex is pale, but the medulla is deep red in color. Pale areas of necrosis may be detected in the pyramids and papillae. Microscopically the hemorrhage may be so severe that the collecting tubules seem to be floating in a pool of blood. The picture suggests that the toxic agent is concentrated in the renal medulla, being excreted in the tubules. Nephrotic lesions and numerous pigment casts in the tubules may be attributed to the accompanying shock. Marked hemorrhage in the renal pelvis is a common feature. The *pituitary* is nearly always soft and hemorrhagic, and infarct-like areas of necrosis are present in the anterior lobe. In one-third of the cases the entire anterior lobe is destroyed. There may be hemorrhage, but no necrosis in the posterior lobe and hypothalamus. The *adrenals* present hemorrhage in half the cases, and often large areas of necrosis. In the *heart* a distinctive feature is severe subendocardial and subepicardial hemorrhage frequently limited to the right auricle. The left auricle is less often hemorrhagic, but mononuclear infiltration is more common, and this may involve the adjoining ventricle. The entire *gastrointestinal tract* is deep red from hemorrhage, but this is most marked in the lower part of the small intestine.

## RICKETTSIA DISEASES

In 1909 H. T. Ricketts described minute bodies in the blood of patients suffering from Rocky Mountain fever and in the tick which carries the disease. In 1910 Ricketts and Wilder found the same minute bodies in the intestinal canal of lice which had fed on typhus patients. These are now known as Rickettsia bodies or simply Rickettsiæ. They are just visible, being from 0.3 to 0.5 micron in diameter. Their filterability is doubtful. They vary in shape, and stain best with Giemsa. It is now known that there are many different varieties of Rickettsiæ. They are all transmitted to man by some insect (arthropod) vector. They grow only in the cytoplasm of living cells, not on artificial culture media; for this reason typhus vaccine is grown on the yolk-sac of developing hen's eggs. In man they live only in the mesothelial cells of the vascular and reticulo-endothelial systems. They cause



a cutaneous rash, and nervous and mental symptoms. The serum of patients contains agglutinins for the *Proteus* group of bacteria. They develop in the gut of the arthropod host, multiply there, and are discharged in enormous numbers in the dejecta. Six are known to be pathologic for man, causing typhus, tsutsugamuihs fever, Rocky Mountain spotted fever, trench fever, rickettsial pox and Q-fever.

**Typhus Fever.** Typhus is an acute infectious fever which used to be one of the great scourges of man. Being carried by the body louse it is seldom seen in ordinary life, but was fearfully prevalent during the First World War, especially in the Balkan States. No disease has been more fatal to the men who have investigated it. Ricketts, Prowazek, Bacot, and many others are among its distinguished victims. Although many microorganisms have been described in connection with typhus, there seems to be little doubt that it is caused by a *Rickettsia* body, *Rickettsia prowazeki*, which is found both in the human patient and in the lice which have been feeding on him.

Zinsser, in his delightful and entertaining *Rats, Lice and History*, remarks that "louse transmission was the great discovery made by Nicolle, which furnished the first powerful weapon for a counter-attack against the disease. It explained the manner in which epidemics are propagated. It removed all mystery from the historic association of typhus epidemics with wars, famines, and wretchedness. But it left unanswered the problem of the smouldering embers of the virus in inter-epidemic periods." For the human louse soon dies on being infected with typhus. The secret reservoir of infection was only recently found to be the domestic rat, transmission from animal to animal being through the agency of the rat flea. If the rat dies and the rat flea is hard put to it to find a new host he may bite man. This is the sporadic case. If the victim is lousy and lives in a lousy community, the result is an epidemic.

The onset of the disease is acute, with high fever, great weakness and prostration, tracheobronchitis with bronchopneumonia, and a macular rash which is often characteristically hemorrhagic. There may be necrosis of the skin.

**Lesions.** The gross pathological changes are not characteristic. There is acute splenic swelling and cloudiness of the organs. The *microscopic changes* are quite characteristic, taking the form of proliferative and thrombotic lesions in the vessels of the skin, the skeletal muscles, the heart, and the central nervous system. It is these which are responsible for the hemorrhagic rash and the occasional necrotic lesions. There is a swelling and proliferation of the vascular endothelium, and at the site of this swelling thrombosis is liable to occur. In Giemsa preparations the swollen endothelial cells may sometimes be seen to be crowded with *Rickettsiæ*. Perivascular accumulations of mononuclear and polymorphonuclear cells are common, and in addition tubercle-like nodules are scattered through the central nervous system. These are produced by neuroglial proliferation, and provide another example of the proliferation which is so characteristic a feature of the microscopic lesions.

In man the *Rickettsiæ* are found in the endothelial cells. In the louse they are confined to the lining epithelium of the gut, where they multiply prodigiously. Beautiful illustrations of the lesions and the *Rickettsiæ* will be found in Wolbach's monograph. Infection is carried by the body louse, which does not become infective until seven days after feeding. The infection is not necessarily caused by bites, for the excreta of the louse are swarming with *Rickettsiæ*, and these, when deposited on the skin, may enter through scratches and abrasions. Bacot died of typhus although he was never bitten. The virus is present in the blood, in the leucocytes and in the blood platelets. It is often stated that it is filterable, but this is probably a mistake. The disease can be transmitted to monkeys and also to guinea-pigs by the subcutaneous injection of infected blood and by the bites of infected lice.

The *Weil-Felix reaction* is a curious example of heterologous antibody action. The blood of typhus patients gives a marked agglutination with many coliform organisms, and particularly with the *Proteus* group. This *Bacillus proteus* reaction is positive by the fifth day in 50 per cent of cases, and soon becomes positive in over 90 per cent of cases. It is therefore of great diagnostic value. Though described by Weil and Felix in 1916 it was previously described by Wilson of Belfast in 1910.

**TSUTSUGAMUSHI FEVER.**—This typhus-like infection, also known as scrub typhus, is endemic in Japan, Malaya and the East Indies. It is caused by *Rickettsia orientalis*, and the disease is transmitted by the bite of an infected larva of certain mites. The habitat of the mite is in rotting vegetation and tall grass, hence the name scrub typhus. Indeed it would be better called mite typhus, just as we may distinguish louse-borne typhus (ordinary typhus), tick-borne typhus (Rocky Mountain spotted fever), and flea-borne typhus. Only in louse-borne typhus is the infection transmitted directly from man to man. A characteristic ulcer usually develops at the site of entry of the infection, associated with local and general lymphadenopathy.

**ROCKY MOUNTAIN SPOTTED FEVER.**—Rocky Mountain fever or spotted fever bears a remarkable resemblance to typhus fever in regard to symptoms, lesions, and bacteriology. It is an acute infection with headache, continued fever, pains in the muscles, and a macular eruption which often becomes hemorrhagic ("spotted fever"), and sometimes necrosis of the skin. It used to be thought that the disease was confined to the northwestern part of the United States (Rocky Mountain region), but it is now known that the infection may be acquired over a considerable part of the United States, east as well as west, and in southern Canada. There is some difference between the lesions in the eastern and western forms of the disease.

The disease is caused by one of the *Rickettsia* group, and is therefore conveyed by an arthropod, this time a wood tick, *Dermacentor venustus*. The disease is confined to regions and seasons (spring and early summer) in which wood ticks abound. As in the case of typhus, laboratory workers may acquire the disease without being bitten by the tick. In such cases the infected material must get on the skin and penetrate through cracks and scratches. The infection can be transmitted to the monkey, rabbit, and guinea-pig. In the guinea-pig the disease is much more severe than when the animal is infected with the *Rickettsia* of typhus, and there is often necrosis of the external genitals. The organism has never been cultivated on artificial media, nor is it filterable. It is always intracellular in the tick. Unlike *Rickettsia prowazeki*, it can be transmitted from one generation of ticks to another without the intervention of man. Washed red and white blood cells can transmit the disease to an animal, although *Rickettsiæ* are almost never seen within these cells, suggesting that the virus may assume a form in which it cannot be demonstrated at present. A vaccine has been prepared from an emulsion of infected ticks. By its use (dose = 4 ticks) the mortality in the Bitterroot Valley, Montana, has been reduced from 90 per cent to 9 per cent.

**Lesions.**—These are very similar to those of typhus fever. The spleen is enlarged, and there may be hemorrhage in the ovaries and testes, but the only characteristic lesions are microscopic. There is the same proliferative arteritis combined with thrombosis. The endothelial cells lining the vessels become greatly swollen and undergo division. Thrombosis, both mural and occluding, occurs on the swollen endothelium. The result of the vascular occlusion is seen in the hemorrhagic rash and the necrotic areas on the skin. In the eastern form of the disease focal brain lesions consisting of axonal swelling and degeneration, together with a proliferative gliosis, are very characteristic; they are never found in the western form. (Lillie.)

**TRENCH FEVER.**—This is the third of the *Rickettsia* diseases, but differs from typhus fever and Rocky Mountain spotted fever in having a mortality so low that nothing is known of the lesions in man. The infection is carried by the body louse, so that the disease affects troops under conditions of trench warfare. It was the

commonest of all the diseases affecting the troops in France during World War I. It is an acute febrile disease characterized by great prostration, severe pain in the muscles and bones ("shin bone fever"), and recurring attacks of fever often at intervals of five or six days ("intermittent fever," "five-day fever"). Pain in the muscles is severe and very characteristic. In many cases there is a red macular rash. It will be seen that the symptoms are not unlike those of typhus and Rocky Mountain spotted fever. A striking feature is the long period during which the patient harbors the infection. Lice have been infected from a patient more than a year after the onset of the disease. The recurrences which sometimes occur many months after the initial attack are thus easy to understand.

Infection can be transmitted from one person to another by the injection of whole blood or of washed red or white corpuscles, but not by the use of serum. The infection is therefore carried in the cells. The Rickettsiae are found in lice which have fed on trench fever patients. The organisms are present in enormous numbers in the excreta of the louse. Infection is due either to bites or to excreta being rubbed into scratches and abrasions.

**RICKETTSIAL POX.**—A new rickettsial disease was recognized in 1946 in New York. Because of an eruption not unlike atypical chickenpox it was named rickettsialpox. The prognosis is uniformly favorable. The initial lesion due to the bite of a tick is a dark red papule. There is mild fever of about one week's duration, a papulo-vesicular rash, sore throat, and in some cases enlargement of lymph nodes and spleen. Knowledge of the lesions is dependent on biopsy material (Dolgopel). The initial lesion resembles that of scrub typhus. The rash is similar microscopically to that of other rickettsial diseases; there is the same cellular infiltration and vascular change. In the lymph nodes the necrosis characteristic of scrub typhus is absent.

Q-fever will be described in the section on Lungs.

#### ADDITIONAL READING

- Acid-fast Bacilli.** BRANCH: *Tubercle*, 1933, **14**, 337. WHITE: *Bull. Johns Hopkins Hosp.*, 1931, **48**, 143.
- Actinobacillosis.** BEAVEN and THOMPSON: *Am. J. Path.*, 1933, **9**, 603. THOMPSON and WILLIUS: *J. A. M. A.*, 1932, **99**, 298.
- Actinomycosis.** COPE: *Brit. J. Surg.*, 1915, **3**, 55; *Actinomycosis*, London, 1938.
- Allergy in Tuberculosis.** WILLIS and WOODRUFF: *Am. J. Path.*, 1938, **14**, 337.
- Anaerobic Streptococci.** McDONALD, *et al.*: *Arch. Path.*, 1937, **23**, 230.
- Bartonella Anemia.** NIVEN: *J. Path. and Bact.*, 1934, **39**, 185.
- Bejel.** HUDSON: *Arch. Path.*, 1936, **21**, 727.
- Blastomycosis.** BAKER: *Am. J. Path.*, 1942, **18**, 479.
- Botryomycosis.** BERGER, *et al.*: *Arch. Path.*, 1936, **21**, 273. KIMMELSTIEL and ODEN: *Arch. Path.*, 1939, **27**, 313. PLAUT: *Arch. Path.*, 1937, **23**, 602.
- Cat Scratch Disease.** DANIELS and MACMURRAY: *Arch. Int. Med.*, 1951, **88**, 736.
- Chronic Miliary Tuberculosis.** AUERBACH: *Am. J. Path.*, 1944, **20**, 121. HOYLE and VAIZEY: *Chronic Miliary Tuberculosis*, London, 1937.
- Coccidioidal Granuloma.** DICKSON: *J. A. M. A.*, 1938, **111**, 1362. PULFORD and LARSON: *J. A. M. A.*, 1929, **93**, 1049.
- Diphtheria.** ANDERSON, *et al.*: *J. Path. and Bact.*, 1931, **34**, 667.
- Epidemic Hemorrhagic Fever.** HULLINGHORST and STEER: *Ann. Int. Med.*, 1953, **38**, 77. MAYER: *Laboratory Investigation*, 1952, **1**, 291. *Military Surgeon*, 1952, **110**, 276.
- General References.** DIBLE: *Recent Advances in Bacteriology*, London, 1931. SCHAMBERG and KOLMER: *Acute Infectious Diseases*, Philadelphia, 1928.
- Ghon Lesion.** FELDMAN and BAGGENSTOSS: *Am. J. Path.*, 1938, **14**, 473.
- Granuloma Inguinale.** MCINTOSH: *J. A. M. A.*, 1926, **87**, 996. PUND and GREENBLATT: *Arch. Path.*, 1937, **23**, 224.

- Inclusion Bodies.** FARBER AND WOLBACH: *Am. J. Path.*, 1932, 8, 123. GOODPASTURE: *Arch. Path.*, 1929, 7, 114.
- Influenza.** HOLMAN: *Am. J. Med. Sci.*, 1936, 191, 426. LAIDLAW: *Lancet*, 1935, 1, 1118. MCCALLUM: *J. A. M. A.*, 1919, 72, 720. OPIE: *Arch. Path.*, 1928, 5, 285. SHOPE: *J. Exper. Med.*, 1931, 54, 349, 373.
- Instability of Tuberculin Reaction.** DAHLSTROM: *Am. Rev. Tuberc.*, 1940, 42, 471.
- Leprosy.** FITE: *Arch. Path.*, 1943, 35, 611.
- Lymphogranuloma Venereum.** COLE: *J. A. M. A.*, 1933, 101, 1069. D'AUNOY AND VON HAAM: *Arch. Path.*, 1939, 27, 1032. D'AUNOY, *et al.*: *Am. J. Path.*, 1935, 11, 737. MATHEWSON: *J. A. M. A.*, 1938, 110, 709. PIERSOL, *et al.*: *Trans. Assn. Am. Phys.*, 1938, 53, 275. STANNUS: *A Sixth Venereal Disease*, London, 1933. TAMURA: *J. Lab. and Clin. Med.*, 1935, 20, 393. THOMPSON: *J. A. M. A.*, 1936, 106, 1869.
- Measles.** FINKELDEY: *Virchows Arch. f. path. Anat.*, 1932, 284, 518. GORDON AND KNIGHTON: *Am. J. Path.*, 1941, 17, 165.
- The Mycoses.** ASHFORD: *Nelson Loose-leaf Medicine*, 1930, 2, 355.
- Parasitism.** ZINSSER: *Rats, Lice and History*, Boston, 1935.
- Pneumococcus.** DOCHÉZ AND AVERY: *J. Exper. Med.*, 1917, 26, 477. HEIDELBERGER AND AVERY: *J. Exper. Med.*, 1923, 38, 73; 1924, 40, 301. RICH AND MCKEE: *Bull. Johns Hopkins Hosp.*, 1936, 59, 171.
- Polomyelitis.** AMOSS, in *Rivers' Filterable Viruses*, Baltimore, 1928. HURST: *J. Path. and Bact.*, 1931, 34, 331.
- Psittacosis.** BEDSON, *et al.*: *Lancet*, 1930, 1, 235. HUTCHISON, *et al.*: *Brit. Med. J.*, 1930, 1, 633. LILLIE: *Nat'l Inst. Health Bull. No. 161*, 1933. RIVERS, *et al.*: *J. Exper. Med.*, 1931, 54, 91, 105.
- Rheumatic Fever.** COBURN AND PAULI: *J. Exper. Med.*, 1932, 56, 609. FRASER: *Lancet*, 1933, 1, 1117; *Arch. Dis. Child.*, 1932, 7, 181. GIBSON AND THOMSON: *Trans. Med.-Chir. Soc., Edinburgh*, 1932-1933, 112, 93. GOULEY AND EIMAN: *Am. J. Med. Sci.*, 1932, 183, 359. GREEN: *Ann. Rheumat. Dis.*, 1939, 1, 86. GROSS AND EHRLICH: *Am. J. Path.*, 1934, 10, 467, 489. KLINGE: *Ergebn. d. allg. Path. u. path. Anat.*, 1933, 27, 1-354; *Virchows Arch. f. path. Anat.*, 1932, 286, 344. RHEA: *Am. J. Path.*, 1933, 9, 719. RICH AND GREGORY: *Bull. Johns Hopkins Hosp.*, 1943, 73, 239. RINEHART AND METTIER: *Am. J. Path.*, 1934, 10, 61. SACKS: *Am. Heart J.*, 1925, 1, 750. VON GLAHN AND PAPPENHEIMER: *Am. J. Path.*, 1926, 2, 235.
- Rhinosporeidiosis.** SHREWSBURY: *J. Path. and Bact.*, 1933, 36, 431. WELLER AND RIKER: *Am. J. Path.*, 1930, 6, 721.
- Rickettsia.** COWDRY: *Arch. Lab. and Clin. Med.*, 1926, 2, 59.
- Rocky Mountain Spotted Fever.** HARRIS: *Am. J. Path.*, 1933, 9, 91. LILLIE: *U. S. Pub. Health Rep.*, 1931, 46, 2840. PARKER: *Arch. Path.*, 1933, 15, 308. WOLBACH: *J. Med. Res.*, 1919, 41, 1.
- Sarcoidosis.** BARRIE AND BOGOCH: *Am. J. Path.*, 1953, 29, 451. CAMERON and DAWSON: *Edinburgh Med. J.*, 1946, 53, 465. ENGLE: *Am. J. Path.*, 1953, 29, 53. HANNESSON: *Brit. J. Tuberc.*, 1941, 35, 88. HARRELL: *Arch. Int. Med.*, 1940, 65, 1003. LONGCOPE: *J. A. M. A.*, 1941, 117, 1321. NICKERSON: *Arch. Path.*, 1937, 24, 19. PINKERTON and IVERSON: *Arch. Int. Med.*, 1952, 90, 456. SCHAUMANN: *Brit. J. Dermat.*, 1936, 48, 399. SNAPPER and POMPEN: *Pseudo-tuberculosis in Man*, Haarlem, 1938. TEILUM: *Am. J. Path.*, 1948, 24, 490.
- Scarlet Fever.** BRODY AND SMITH: *Am. J. Path.*, 1936, 12, 373.
- Staphylococci.** BURNET: *J. Path. and Bact.*, 1929, 32, 717. DOLMAN: *J. A. M. A.*, 1933, 100, 1007. RYLE: *Guy's Hosp. Rep.*, 1930, 80, 137.
- Streptococci.** BROWN: *Rockefeller Inst. Med. Res., Monog. No. 9*, 1919. DICK AND DICK: *J. A. M. A.*, 1927, 89, 1135. GAY: *J. A. M. A.*, 1931, 97, 1193. LANCEFIELD AND HARE: *J. Exper. Med.*, 1935, 61, 335. McLEOD: *Med. Res. Council, System of Bacteriology*, 1929, 2, 44. OKELL: *Lancet*, 1932, 1, 761, 815, 867. RYLE: *Guy's Hosp. Rep.*, 1931, 81, 1. TILLET AND GARNER: *J. Exper. Med.*, 1933, 58, 485.
- Streptococcal Infection.** MALLORY AND KEEFER: *Arch. Path.*, 1941, 32, 334.
- Spread of Tuberculosis.** LONG: *Am. J. Path.*, 1941, 17, 697.
- Syphilis.** CHESNEY: *Harvey Lectures*, 1929-1930, p. 103. INGRAHAM: *Am. J. Syph.*, 1932, 16, 155. KAST AND KOLMER: *Am. J. Syph.*, 1929, 13, 419. LEVADITI: *Ann. de l'Inst. Pasteur*, 1928, 42, 475. STOKES: *Modern Clinical Syphilology*, Philadelphia, 1934.

- Tetanus.** ABEL: *Science*, 1934, **79**, 63, 121. ABEL, *et al.*: *Bull. Johns Hopkins Hosp.*, 1938, **63**, 373. ASHURST: *Arch. Surg.*, 1920, **1**, 407. BARNES AND TRUETA: *Lancet*, 1941, **1**, 623.
- Trench Fever.** ARKWRIGHT, *et al.*: *J. Hyg.*, 1919, **18**, 76.
- Tsutsugamushi Fever.** ALLEN AND SPITZ: *Am. J. Path.*, 1945, **21**, 603.
- Tuberculoïd Granulomas.** McDONALD and WEED: *Am. J. Clin. Path.*, 1951, **21**, 223. SYMMERS: *Am. J. Path.*, 1951, **27**, 493.
- Tuberculosis.** BLACKLOCK: *Med. Res. Council, Spec. Rep. Series*, No. 172, 1932. CORBETT: *The Causes of Tuberculosis*, Cambridge, 1917. DUBOS and DAVIS: *J. Exper. Med.*, 1946, **83**, 409. FRIED: *Arch. Path.*, 1931, **12**, 689. GUON: *The Primary Lung Focus of Tuberculosis in Children*, New York, 1916. KOCH: *Klin. Wehnschr.*, 1882, **19**, 221 (English translation in *Am. Rev. Tuberc.*, 1932, **25**, 285). LURIE: *J. Exper. Med.*, 1932, **55**, 31; 1933, **57**, 181. MEDLAR: *Am. J. Path.*, 1926, **2**, 275, 291. OPIE: *Am. Rev. Tuberc.*, 1924, **10**, 249. RICH: *The Pathogenesis of Tuberculosis*, Springfield, 1944. RICH AND McCORDOCK: *Bull. Johns Hopkins Hosp.*, 1929, **44**, 273. WILSON: *Med. Res. Council, Spec. Rep. Series*, No. 182, 1933.
- Tuberculosis, Primary, in Adults.** HEIMBECK: *Tubercle*, 1936, **18**, 97. MYERS, *et al.*: *Arch. Int. Med.*, 1937, **59**, 1. SOPER AND AMBERSON: *Am. Rev. Tuberc.*, 1939, **39**, 9.
- Tularemia.** FRANCIS: *Medicine*, 1928, **7**, 411. LILLIE, *et al.*: *Nat. Inst. Health Bull.* No. 167, Washington, 1936. SIMPSON: *Tularemia*, New York, 1929.
- Typhoid Fever.** GAY: *Typhoid Fever Considered as a Problem of Scientific Medicine*, New York, 1918. GOODPASTURE: *Am. J. Path.*, 1937, **13**, 175. MALLORY: *J. Exper. Med.*, 1898, **3**, 611. MALLORY AND LAWSON: *Am. J. Path.*, 1931, **7**, 71.
- Typhus.** WALBACH, *et al.*: *The Etiology and Pathology of Typhus*, Cambridge, Mass., 1922. ZINSSER: *Rats, Lice and History*, Boston, 1935.
- Undulant Fever.** HUDDLESON: *Brucellosis in Man and Animals*, New York, 1939. PARSONS, *et al.*: *Am. J. Path.*, 1939, **15**, 634. RABSON: *Am. J. Clin. Path.*, 1939, **9**, 604. SHARP: *Arch. Path.*, 1934, **18**, 72.
- Viruses.** COWDRY: *Arch. Path.*, 1934, **18**, 527. GOODPASTURE: *Harvey Lectures*, 1931, **25**, 77. LAIDLAW: *Virus Diseases and Viruses*, London, 1938. LEDINGHAM: *Brit. Med. J.*, 1932, **2**, 953; *Bull. Johns Hopkins Hosp.*, 1935, **56**, 247, and **57**, 32. RIVERS: *Am. J. Path.*, 1928, **4**, 91; *Am. J. Med. Sci.*, 1935, **190**, 435; *Arch. Neurol. and Psychiat.*, 1932, **28**, 757; *Filterable Viruses*, Baltimore, 1928; *Harvey Lectures*, 1933-1934, p. 220; *Viruses and Virus Diseases*, California, 1939 (*Lane Medical Lectures*). VAN ROOYEN AND RHODES: *Virus Diseases of Man*, London, 1940. STANLEY: *Science*, 1935, **81**, 644.
- Whooping Cough.** RICH: *Bull. Johns Hopkins Hosp.*, 1932, **51**, 347.
- Yellow Fever.** KLOTZ AND BELT: *Am. J. Path.*, 1930, **6**, 655.

## Chapter

# 8

## DISEASES CAUSED BY ANIMAL PARASITES

**PATHOGENIC** parasites are of common occurrence even in temperate countries, and when the tropical parasites are included we meet some of the most widespread diseases of mankind. Many of the parasites pass through a complicated life cycle, which adds to the interest (and the difficulty) of the subject. Very few parasites pass their life cycle in only one host. The eggs produced in the body of a man or animal do not develop in the same body. They may develop into larvæ in the soil, or they may be ingested by another host and develop there. The *definitive host* is the host of the adult parasite (sexual cycle), and the *intermediate host* is the host of the embryo (asexual cycle). Thus man is the definitive host of the common tapeworms, but the intermediate host of the malarial parasite. A *vector* is a means of conveying parasites to a new host; vectors may be vegetable or animal foodstuffs or insects. An insect vector may also be a host. A knowledge of the life history of the parasite outside as well as inside the patient is essential if the disease is to be attacked rationally and successfully.

The teacher of pathology commonly finds that the student experiences great difficulty in mastering the subject of the animal parasites, for which he is apt to acquire a marked distaste. This is because he is overwhelmed by the number of parasites and the need of learning the exact dimensions of the male and female of each species. For this reason only a limited number of parasites will be described here, and emphasis will be laid on their biological behavior and the disturbances they produce in man rather than on their structural detail. The latter can be obtained in any book on parasitology.

The subject will appear less vast and confusing if the beginner will realize the following facts. Disease-producing parasites belong to two great groups, protozoa (unicellular organisms) and worms. There are four important protozoal parasites, causing malaria, Leishmaniasis, trypanosomiasis, and amoebic dysentery. The worms are divided into flukes, tapeworms and round worms. Of these one fluke will be considered, four tapeworms, and six round worms. A wealth of information and superb illustrations will be found in the *Atlas of Pathology of Tropical Diseases* by Ash and Spitz.

It may be well to point out that parasitism, whether animal or bacterial, is not necessarily a matter of invader and defender. The point of view of the parasite must also be considered. The host provides the parasite with all the comforts of life. It is really a biological accident if some metabolic incompatibility between host and parasite should lead to the manifestations

of disease. The successful parasite is the one which does not jeopardize the survival of the host, because in so doing it jeopardizes its own survival.

## PROTOZOA

**Entamoeba Histolytica.**—This is the cause of amebic dysentery, which is considered in connection with diseases of the intestine. The ameba is a single cell from 20 to 30 microns in diameter, with an outer hyaline ectoplasm and an inner granular endoplasm. Movement is effected by an outflowing of the outer hyaline zone in the form of pseudopodia into which flows the granular endoplasm. The parasite is recognized by its mobility, which can be studied in an absolutely fresh specimen of feces on the warm stage of the microscope. Differentiation from the harmless *Entamoeba coli*, which also occurs in the stools, is difficult; *Entamoeba histolytica*

frequently contains red blood cells and vacuoles, whereas *Entamoeba coli* does not. In chronic cases, such as are seen in temperate countries, there are often no mobile forms, for under unfavorable conditions the ameba becomes globular, shrinks in size and is converted into a cyst measuring 10 to 15 microns and having an outer capsular layer. The cystic forms of *Entamoeba histolytica* and *Entamoeba coli* are much more easily differentiated than the active forms, for the former cysts have four nuclei when fully developed.

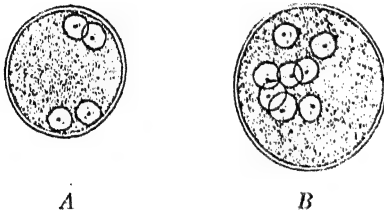


FIG. 87.—A, Cyst of *E. histolytica* stained with iodine, showing 4 nuclei; B, cyst of *E. coli* with 8 nuclei. (Blacklock and Southwell, Human Parasitology, H. K. Lewis & Co.)

opened, the latter have eight nuclei. (Fig. 87.) The cysts are the infective form of the parasite, for the active form is killed by the gastric juice as it passes through the stomach. Multiplication is by direct division; there is no sexual stage.

The ameba is arrested in the colon, where it may invade the mucosa and set up the acute inflammation of dysentery. From the intestine it may invade the radicles of the portal vein, be carried to the liver, and there give rise to amebic abscesses. The disease is spread from person to person and by flies. While fly infection must be guarded against in the country, in the city the chief danger is from food handlers who are chronic carriers, and in whose stools the cysts may be found. Amebic dysentery is endemic in the tropics, but isolated cases and occasional epidemics occur in England, the United States, Canada, etc. These can usually be traced to food carriers. Intestinal amebiasis is a common condition; indeed it is estimated that 10 per cent of the population of the United States (3 per cent in large cities) harbor *Entamoeba histolytica* in the intestine. But we must distinguish between amebiasis and dysentery. As Lynch remarks: "Amebic dysentery is the comparatively uncommon acute phase or end-result of intestinal amebiasis." It is not known what upsets the usual balance between parasite and host.

**BALANTIDIUM COLI.**—This is a ciliated protozoön parasite which, like *Entamoeba histolytica*, occurs in the bowel in an active or trophozoite form and in an encysted form. The cysts are passed in the stools and are infective, while the active form dies outside the body. In the intestine the encysted parasites develop into trophozoites, which invade the mucous membrane and produce ulcers, chiefly in the large intestine, but occasionally in the lower part of the small intestine. The ulcers resemble those of amebic dysentery, and the symptoms are dysenteric in type.

**Plasmodium Malariae.**—The malarial parasite was discovered by Laveran in 1880, and in 1895 Ronald Ross showed that the disease was transmitted by the anopheles mosquito. These are the two great landmarks in the fight against one of the most important diseases which afflict man. The word malaria is of interest. It means bad air (*malo*, bad; *aria*, air), and is a reminder of the days when the disease was thought to be transmitted by the miasmatic vapors of marshes. It was the mosquitoes, not the miasmas, that lived in the marshes. Among all tropical diseases malaria is supreme. It is the most persistent, the most destructive, the most widespread, and the most difficult to control. Osler, indeed, has called it the greatest single destroyer of the human race. Those peoples touched by the shaking finger of malaria have undergone a gradual decadence, as may be seen in the history of Greece and Rome.

There are three forms of malaria: benign tertian caused by *Plasmodium vivax*, quartan caused by *Plasmodium malariae*, and malignant tertian or subtertian caused by *Plasmodium falciparum*. The third form is also known as estivo-autumnal, because in subtropical countries it occurs principally in the later summer and autumn. In benign tertian the characteristic chill or attack of fever occurs every forty-eight hours (every other day) and lasts only two or three hours, in quartan it occurs every seventy-two hours (every third day), and in the malignant tertian it occurs every forty-eight hours but is prolonged for several hours with a plateau rise of temperature making the attacks seem closer together. The distribution is as wide as that of the anopheles mosquito; it embraces the tropics, the southern United States, and many parts of Italy, Greece, the Balkans, etc. The disease may recur after one or several years, for the parasites hide in the spleen and bone-marrow, and come out when the patient goes to a cold climate. The parasite passes an asexual stage of its life cycle in man and a sexual stage in the mosquito. (See Plate IV.)

**Asexual Stage.**—The tertian, the commonest form, will be taken as an example. When an infected mosquito bites a man it injects a large number of rod-shaped parasites known as *sporozoites* or spores into the blood stream. One sporozoite attaches itself to an erythrocyte, penetrates it, becomes rounded, and enters on the stage of asexual development. A multitude of names have been given to the various steps of the process by zoölogists, but these will be omitted for the most part. The parasite, being a cell, consists of a nucleus and cytoplasm. It forms a rounded body within the red blood corpuscle, the nuclear chromatin staining red with Wright's stain and the cytoplasm blue. The parasite often assumes a signet-ring form, with red nucleus at one side of the ring. The parasite grows rapidly at the expense of the hemoglobin, so that the red cell becomes pale and swollen.



The parasite contains dark brown granules of pigment derived from the hemoglobin and commonly called malarial pigment. The pigment is manufactured by the parasite, and does not give the reaction for hemosiderin. The cytoplasm of the erythrocyte shows a fine red stippling (Schüffner's dots) which is not seen in the quartan and estivo-autumnal forms (see colored plate). Asexual division then occurs. The nuclear chromatin divides into 18 or 20 fragments (in the tertian type), and the cytoplasm is divided so as to surround each of these. The new bodies are arranged around the periphery of the erythrocyte to form a *rosette*. The rosette breaks up into a number of new individuals or *merozoites*, and at the end of forty-eight hours these are discharged from the ghostly remains of the erythrocyte into the blood stream. This process is repeated in all the infected erythrocytes at practically the same time, and it is the sudden outpouring of foreign protein into the blood which is the cause of the chill and fever. Each merozoite now becomes attached to and enters a fresh erythrocyte, and the whole process is repeated. It is evident that a profound anemia may be produced in this way.

*Sexual Stages*.—Some of the merozoites develop into parent sexual cells or *gametocytes* which are set apart for sexual reproduction. In the malignant tertian type these have a characteristic crescentic form. If the

#### EXPLANATION OF PLATE IV.<sup>1</sup>

Partly schematic. Drawn and rearranged by Williams, partly from Muir and Ritchie, partly from Kolle and Hetsch and partly original. Giemsa's stain.

The asexual forms show cycle of the organism in the red blood cells of the human host. They show schematically the time of fever and the day of segmentation.

*Tertian type.*

FIG. 1.—Segmented organism.

FIG. 2.—Young ring form in cell and a young form on surface.

FIG. 3.—Growing schizont; irregular form due to great motility; beginning pigment formation; red blood cell becoming paler.

FIG. 4.—Larger schizont. Red cells pale and stippled (Schüffner's dots).

FIG. 5.—Nucleus divided into four clumps.

FIG. 6.—Further division of chromatin and formation of irregular rosette. Pigment finely granular in center.

FIG. 7.—Segmentation. Note 18 merozoites (usually 16).

*Quartan type.* Shows following differences from tertian: Slightly larger, fewer segments (usually 8), and more regular. Pigment coarse. Red blood cells unaltered. Segmentation every seventy-two hours.

*Malignant tertian type.* Shows following differential points: Merozoites smaller and more numerous (32); organism less motile with less pigment. Red blood cells smaller and greenish color (in fresh cells).

*Sexual forms.* Show cycle of development in mosquito.

FIG. 1 (*A* to *E*).—Male (♂) and female (♀) forms of tertian type formed in human blood; *F*, flagellation of male type in stomach of mosquito; *G*, *H*, changes in female type and fertilization in stomach of mosquito.

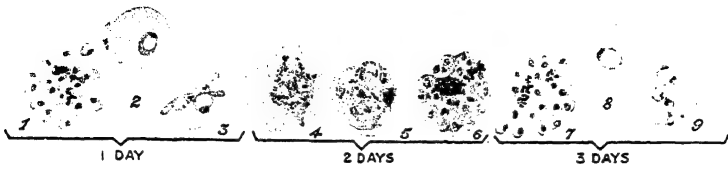
FIG. 2.—Development of sporocyst within mosquito. Liberation of sporozoites which find their way to the salivary gland.

FIG. 3.—Sexual forms of malignant tertian type found in human blood, showing development of sickle-shaped bodies.

<sup>1</sup> From Park and Williams: Pathogenic Microorganisms.

# PLATE IV

## A. PLASMODIUM VIVAX



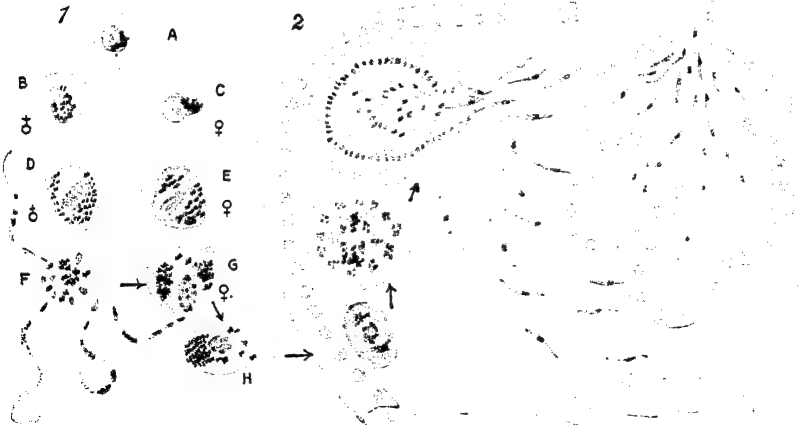
## B. PLASMODIUM MALARIAE (QUARTAN)



## C. PLASMODIUM FALCIPARUM



## D. DEVELOPMENTAL CYCLE IN THE MOSQUITO



## E. SEXUAL FORMS OF PLASMODIUM FALCIPARUM



gametocytes are taken into the stomach of the female anopheles mosquito they enter upon the sexual stage of the life cycle. The gametocytes are male and female. From the male gametocytes are protruded a number of whip-like bodies resembling spermatozoa. These are detached and form the *male gametes*. The female gametocyte loses some nuclear chromatin and becomes the *female gamete*. One male gamete then enters a female gamete and conjugation takes place. The impregnated cell is called a *zygote*. The zygote burrows through the epithelium of the gut and forms a cyst within which the nucleus divides into hundreds of rod-like bodies, the *sporozoites*. The entire process occupies about twelve days. The sporozoites make their way to the salivary glands, and when the mosquito bites a person they are injected into the blood stream, where the asexual cycle is once more repeated.

The sexual cycle is needed for the rejuvenation and continued existence of the parasites. But without the assistance of this phase they may live in the internal organs (chiefly the spleen) of the patient for months or even years without giving rise to symptoms. He may move to a temperate country where there are no mosquitoes, quite unconscious that he is still a sufferer from the disease. Then an exposure to cold or some lowering of the vitality may bring on a typical pyrexial attack with numerous parasites in the peripheral blood stream.

*Morbid Anatomy.*—At autopsy the two most striking changes are a slate-colored or blackish pigmentation of the abdominal organs and great enlargement of the spleen. The discoloration is due to malarial pigment which resembles melanin in color. It contains iron but does not give the Prussian blue reaction. The spleen is very large, and in acute cases it is extremely soft and diffuent, but in chronic cases it becomes very hard. Microscopically the parasites are seen in the capillaries and there are great deposits both of malarial pigment and hemosiderin. In the occasional acutely fatal case the capillaries are stuffed with parasites. This is best seen in the brain, where the condition may be responsible for coma. Microscopically there is widespread vascular injury, evidenced by fatty degeneration of the endothelium, ring hemorrhages in the brain, and hemorrhagic necrotizing lesions in the myocardium, adrenals, etc. The capillaries of the brain are stuffed with parasitized red corpuscles (Fig. 88), a condition which may result in coma. A fundamental feature of the disease is a marked slowing of the capillary circulation, especially in the brain. This is due to an altered physical quality of the parasitized red corpuscles, which, particularly in the subtertian form, become sticky and adhere to the vessel walls. As a result of this the red cells become agglutinated and form capillary thrombi. There is moreover "blocking" of the reticulo-endothelial system by the liberated pigment. The pigment deposits are most marked in the spleen, liver, and bone-marrow, much of the pigment being within the swollen reticulo-endothelial cells of these organs. In the late stages the spleen may be greatly fibrosed. The enlarged spleen may be ruptured even by slight trauma, a point of medico-legal importance.

**BLACKWATER FEVER.**—Blackwater fever is a complication of malignant tertian malaria characterized by the passage of red or almost black urine. In severe cases

death is the rule. There is a rapid and massive destruction of red blood cells, which may fall as much as 2,000,000 in number in twenty-four hours. The result is hemoglobinemia, hemoglobinuria, intense jaundice, anuria, and frequently death. Methemoglobin is responsible for the very dark color of the urine. The spleen is greatly enlarged, bright red and velvety. The administration of quinine may precipitate an attack. Blackwater fever appears to be an allergic response to reinfection with the parasite of malignant tertian. Most people develop a certain degree of immunity, but a few become allergic. Injection of a suspension of ground-up parasites into the skin of such persons produces an allergic reaction. Quinine liberates the allergen from the parasites. The acute manifestations are in the nature of anaphylactic attacks.



FIG. 88.—Parasitized red cells in capillaries of the brain.  $\times 1000$ .

**TRYPANOSOMES.** Trypanosomes are spindle-shaped protozoan parasites characterized by a macronucleus and a micronucleus, an undulating membrane, and a flagellum. (Fig. 89.) They therefore belong to the group of the flagellates, and vary in length from 10 to 30 microns. The macronucleus is in the center of the



FIG. 89.—*Trypanosoma gambiense*.  $\times 1500$ .

parasite, while the micronucleus is a small mass of chromatin at one end. The undulating membrane is a wavy structure which runs like a fin along the length of the parasite. The flagellum arises from the micronucleus, passes along the undulating membrane, and is prolonged as a free structure which waves about so that the parasites are actively motile. Sexual development occurs in an invertebrate host, the tsetse fly, which transmits the infection from one person to another. Asexual reproduction is by means of longitudinal division in the blood of the intermediate host, *i. e.*, man and many wild animals. There are many varieties of trypanosomes and many tsetse flies, but only two are concerned in the production of serious disease. Trypanosomiasis, the disease caused by trypanosomes, is confined to tropical Africa.

**ANIMAL TRYPANOSOMIASIS (NAGANA).**—This is caused by *Trypanosoma brucei* (named after Sir David Bruce who discovered it), and the intermediate host is the tsetse fly, *Glossina morsitans*. The wild animals (deer, etc.) act as a reservoir for

the infection, although they suffer no symptoms, but when domestic animals (horses, cattle) are taken into the fly belt they are at once infected and the disease is extremely fatal.

**HUMAN TRYPANOSOMIASIS (AFRICAN SLEEPING SICKNESS).**—The human disease is caused by *Trypanosoma gambiense* (called after the Gambia River in which district the fever is prevalent), and is carried by the tsetse fly, *Glossina palpalis*. The trypanosomes live in the blood, causing fever, weakness, emaciation, and enlargement of the cervical and other lymph nodes. It is only later that they invade the central nervous system and cause true sleeping sickness with its characteristic lethargy and coma. The trypanosomes are found in the blood during attacks of fever, in the lymph nodes at any time, and in the cerebrospinal fluid when symptoms of sleeping sickness have developed. The brain lesions are foci of round-cell perivascular infiltration much like those of general paresis of the insane.

**CHAGAS' DISEASE.**—Chagas' disease is a form of trypanosomiasis occurring in South America. Unlike the African form these trypanosomes (*Trypanosoma cruzi*) penetrate the

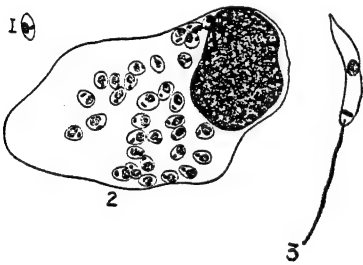


FIG. 90

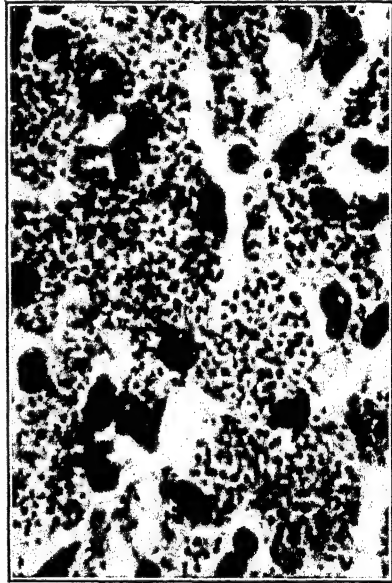


FIG. 91

FIG. 90.—Leishmania. 1, Individual parasite; 2, mass of parasites in a macrophage; 3, flagellate form. (Blacklock and Southwell, Human Parasitology, H. K. Lewis & Co.)

FIG. 91.—Reticulo-endothelial cells of lymph node packed with histoplasma capsulatum.  $\times 510$ . (From a section of Dr. W. A. D. Anderson.)

tissue cells, lose their flagellum, and develop into round leishmania-like bodies about 4 microns in diameter which divide repeatedly and fill the cell. After this intracellular multiplication the rounded bodies develop a flagellum and emerge in the circulation. Various bugs constitute the definitive host. The symptoms of Chagas' disease depend upon the organs the cells of which are penetrated by the parasites, *e. g.*, heart, brain (neuroglia cells), kidney, adrenal, thyroid. The general symptoms include anemia, enlarged lymph nodes, and fever.

**LEISHMANIASIS.**—This tropical disease is caused by the Leishmania group of flagellates, *i. e.*, a parasite which may lose its flagellum and develop into a small, round or oval body about one-half the size of a red blood cell, containing two nuclear bodies, one much smaller than the other, which stain red with the Leishman and other Romanowsky stains. Only the leishmania form occurs in man, the flagellate

form being found in the gut of certain insects which have fed on an infected patient, or in culture of his infected blood. Leishmaniasis occurs in two clinical forms, visceral and cutaneous.

*Visceral leishmaniasis*, commonly known as *kala-azar*, is caused by *Leishmania donovani*. It is characterized by extreme enlargement of the spleen, moderate enlargement of the liver, progressive anemia and marked leucopenia. It is one of the most important causes of splenomegaly in the tropics. The disease is prevalent among children and young adults in India, China, and the Mediterranean countries. The parasites crowd the reticulo-endothelial cells of the spleen, liver, and bone-marrow, but are extremely difficult to find in the blood. They are readily demonstrated in smears made from a splenic puncture, being both intracellular and extracellular. (Fig. 90.) The parasites develop in the gut of the sand-fly (*Phlebotomus*) but it is not certain what part that insect plays in conveying infection. Smears from the nasal cavities and tonsils of patients show Leishman-Donovan bodies, the tonsils being massively infected. This is probably an important method of transmission, perhaps the most important.

*Cutaneous leishmaniasis*, known also as oriental sore, Delhi boil, Aleppo boil, etc., occurs not only in the regions where the visceral form is prevalent, but also in Central and South America. The parasite is morphologically and culturally identical with *L. donovani*. The lesion, which is generally single, takes the form of a chronic sore which heals spontaneously in the course of a year. It consists of a dense accumulation of histiocytes which contain large numbers of *Leishmania*.

**TOXOPLASMOSIS.** This disease is caused by a protozoan parasite, *Toxoplasma*, of crescentic shape, and measuring 7 microns in length and from 2 to 4 microns in width, although in sections of fixed tissues they may be considerably smaller. The parasite is of wide distribution in animals, occurring in the dog, mouse, rat, rabbit, etc. Very few human cases have been reported, mostly in infants. Infection is probably acquired by man from infected animals. In infants transmission appears to be from the mother, although she shows no evidence of the disease.

In infants the chief lesion is an encephalitis. Microscopically small necrotic and granulomatous lesions are found, the nerve cells being crowded with the parasites. In adults the lungs show foci of consolidation, the cells lining the alveoli being swollen and filled with parasites, whilst the alveolar spaces are occupied by an exudate of mononuclear cells. The blood contains neutralizing antibodies. The infection can be transmitted from the human lesions to experimental animals.

## WORMS OR HELMINTHS

The parasitic worms may be divided into flat worms and round worms. The flat worms are subdivided into flukes and tapeworms. Only the more important of the disease-producing worms will be considered.

**FLUKES.**—The flukes are small, flat, leaf-shaped, unsegmented worms. Liver flukes are common parasites of sheep and cattle, living in the bile ducts and producing inflammation of the liver. Infestation of the liver in man is very prevalent in China, where it is caused by *Clonorchis sinensis* (Chinese liver fluke) (Fig. 92). *Fasciola hepatica* (sheep liver fluke) is met with in sheep-raising countries. The lung fluke (*Distomum pulmonis*) is a common parasite in China and Japan where it is an important cause of hemoptysis; the ova are found in the blood-stained sputum.

**SCHISTOSOMIASIS.**—This is the most common and most important of the diseases caused by flukes. Three of the flukes are pathogenic to man: *Schistosoma mansoni* and *S. japonicum* involving chiefly the liver and

intestine, and *S. hematobium*, often known as *Bilharzia hematobia*, involving the bladder. *S. mansoni* is distributed widely throughout the northern part of South America and also in Africa, *S. japonicum* in Japan and the East Indies, and *S. hematobium* in Africa, particularly along the Mediterranean coast. The ova are discharged into water and taken up by a water snail, the intermediate host, from which escape large numbers of active embryos or cercariæ. These penetrate the skin of persons while bathing. The cercariæ of non-pathogenic flukes may penetrate the skin, causing an intense inflammatory reaction known as swimmer's itch.

The cercariæ enter the venous circulation, and reach their final habitat, the mesenteric veins in the case of *S. mansoni* and *S. japonicum*, the vesical plexus in the case of *S. hematobium*. During the period of migration through the lungs there may be asthma, transient infiltrations in the lungs radiologically, and eosinophilia in the blood. The embryos develop into adult flukes about 1 cm. in length in the aforementioned veins, where they may live for years, continually producing new ova. It is these ova which are responsible for the symptoms, dysentery in *S. mansoni* and *S. japonicum* infections, hematuria in *S. hematobium* infections. Moreover it is from the ova that identification of the species is made. *S. mansoni* has a prominent lateral spine, *S. japonicum* a rudimentary lateral spine, and *S. hematobium* a long terminal spine. The severity of the disease is conditioned by the daily output of ova. In the case of *S. japonicum* this is 50 to 30, in *S. hematobium* it is 20 to 30, and in *S. mansoni* it is only 1 to 4.

The ova of *S. mansoni* and *S. japonicum* are deposited in the intestine, where they produce an inflammatory reaction with polypoid overgrowths and dysenteric symptoms. Carcinoma of the colon is a late sequel. Rectal biopsy, and in particular examination of the second valve of Houston, is of greater value than the search for ova in the stools. Microscopically the response is at first leucocytic and eosinophilic, but later the lesions take the form of pseudotubercles with epithelioid cells and giant cells surrounding the necrotic ovum, and final fibrosis. The ova pass readily in the portal circulation to the liver, where they cause the development of portal cirrhosis, rapid in the case of *S. japonicum*, slow in *S. mansoni* on account of the smaller number of ova.

*S. hematobium* (bilharzia) causes widespread disease in Egypt and other parts of northern Africa. The population of Egypt is 12,000,000; 6,000,000 of these are infected, and 1,000,000 are bedridden owing to the disease. The flukes live in the pelvic and vesical veins, and the ova are laid in the wall of the bladder and rectum, where the sharp terminal spine produces an intense reaction. Chronic cystitis and hematuria result. Polypoid



FIG. 92.—*Clonorchis sinensis*.

masses are formed in the bladder, and these may become the starting-point of carcinoma. In Egypt carcinoma of the bladder is said to be 10 times commoner in those suffering from schistosomiasis. Pulmonary lesions are found in some 33 per cent of cases (Shaw and Ghareeb). The ova become impacted in the pulmonary arterioles, causing an acute necrotizing arteriolitis, as a result of which the ova escape into the lung and produce a parenchymatous tubercle. In the great majority of cases only a few ova reach the lungs, and only a few tubercles are formed. When the infestation is heavy there may be an obliterative arteriolitis, which in rare cases gives a clinical picture of Ayerza's disease with death from congestive heart failure.

**Cestodes or Tapeworms.**—There are four tapeworms of importance in human pathology.

Three of these pass an adult stage in the intestine of man and a cystic stage in an intermediate host. They are known as the beef tapeworm (*Tænia saginata*), the pork tapeworm (*Tænia solium*), and the fish tapeworm (*Diphyllobothrium latum*). The fourth (*Tænia echinococcus*) passes the cystic stage in man (the intermediate host) and the adult stage in the dog; this is the one which causes hydatid disease, and is the only really dangerous member of the group.

**TÆNIA SAGINATA (TÆNIA MEDIO-CANELLATA).**—The beef tapeworm is the common tapeworm of the United States and Canada. It is the largest tapeworm and it has the largest intermediate host. It consists of a tiny head or scolex and segments or proglottides. (Fig. 93.) The head is 2 mm. in diameter and possesses four suckers by which it adheres to the intestinal mucosa.

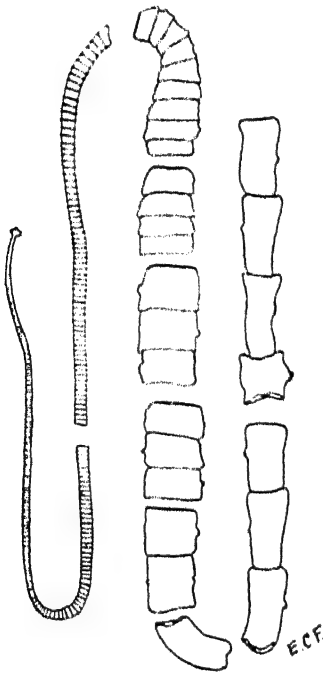


FIG. 93.—Strobila of *Tænia saginata*. Two-thirds natural size. (After Leuckart, *Parasiten des Menschen*.)

It has no hooks. The worm may be 30 feet long and possess some 2000 proglottides. The proglottides are crowded with eggs, and as these become mature the segments break off and are discharged in the feces. When taken up by cattle the ova develop into embryos which migrate to the muscles and there develop into cysticerci. If the beef from an infected cow is eaten imperfectly cooked or in a raw state human infection will result. The diagnosis is made by finding the segments in the feces. The worm, which is usually single, causes wonderfully little disturbance in spite of its great length.

**TÆNIA SOLIUM.**—The pork tapeworm is much rarer than *Tænia saginata*. It is usually under 10 feet in length and resembles *Tænia saginata*.



The head, however, is armed with a double row of hooks. Generally only one worm is found (*solium* means single), but in a few instances there may be two or three. The pig is the intermediate host, its muscles contain large numbers of *cysticercus cellulosa*, and man is infected by eating imperfectly cooked "measly" pork. The eggs may be swallowed owing to self-infection and occasionally the embryos invade the body and develop into the larval cystic form, man thus acting as the intermediate host. This does not occur with *Tænia saginata*. The *cysticercus cellulosa* thus formed may be present in large numbers in the brain, meninges, eye, muscles, and other organs. The larval worm is inverted and the epithelium of the highly tortuous canal of the body becomes continuous with the epidermis covering the outside of the cyst. (Fig. 94.) MacArthur has shown that

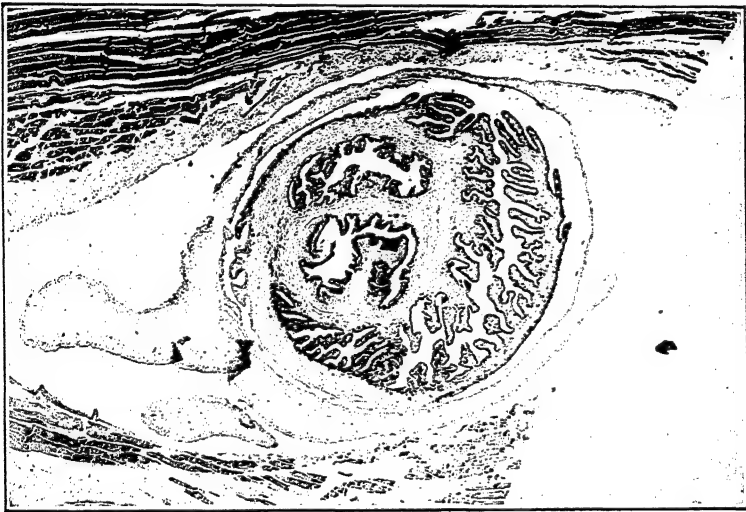


FIG. 94.—*Cysticercus cellulosa* showing continuity of epithelium on surface and that lining body canal.  $\times 22$ .

many soldiers who develop idiopathic epilepsy some years after serving in the tropics are really sufferers from cerebral cysticercosis. In the Millbank Military Hospital in London there were 20 cases in one year. The parasites may be present for years before symptoms develop, for they are tolerated while alive, but act as foreign irritants when they die. They become calcified, and can be seen in radiographs of the muscles. As a rule there is no history of intestinal infection in these cases of cerebral cysticercosis *cellulosa*.

**DIPHYLLOBOTHRIUM LATUM (BOTHRIOCEPHALUS LATUS).**—The fish tapeworm has from 3000 to 4000 segments filled with eggs. The eggs are discharged from the ripe proglottides, but only empty and shrivelled segments are shed, in this respect differing from the other two tapeworms. It follows that in stool examinations the presence of ripe segments indicates *Tænia saginata* or *Tænia solium*, the presence of eggs indicates *Diphyllo-*

*bothrium latum*. The average output of eggs in the stool per day is 1,000,000. The tiny head is flattened and does not possess suckers or hooks but is provided with two longitudinal suckorial grooves. When the ova are discharged they develop into free-swimming larvæ and these are taken up by small water crustaceæ which are in turn devoured by some of the larger fish (pike, perch, etc.), where they invade the muscles and pass into the cysticercus stage.

The geographical distribution is important. It used to be found principally among the fish-eating peoples in the Scandinavian countries, Russia, and in parts of Asia, but lately it has been imported into the United States and Canada, and is now indigenous in the districts around the Great Lakes and Lake Winnipeg. The fish in these lakes are probably infected from dogs, who also harbor the parasite. If the fish are properly cooked there is no danger.



FIG. 95.—*Tania solium* cysts in measly pork. (Kindness of Dr. J. C. Colbeck).

A large number of the worms may be found in one person. In 999 out of 1000 infected persons it is a harmless parasite, provided that the patient is unaware of its presence, although a mild hemolytic anemia is common. In very exceptional cases the patient may develop a severe anemia identical in type with pernicious anemia, but this is seldom seen even in fish-eating communities where the infection is extremely

prevalent; only in Finland is the anemia at all common.

**TAENIA ECHINOCOCCUS.**—This tapeworm is entirely different from the others. It is extremely small, measuring only 5 mm. in length, and possesses only 3 proglottides. The cystic stage is passed in man and many other animals and the adult stage in the intestine of the dog, where there may be hundreds of worms. Man therefore serves as the intermediate host. Human infection is usually due to eating unboiled vegetables soiled by the excreta of dogs. The dogs are infected by eating the flesh of infected sheep. Hydatid disease, as the human infection is termed, is most prevalent in Australia, South America, and other great sheep-raising countries, where dogs and men come into very close contact. Syria has perhaps the largest incidence. Iceland used to be a hot-bed of the disease, but during recent years it has been nearly eradicated by hygienic measures.

When the eggs are swallowed by man they develop into embryos which penetrate the wall of the bowel and are carried in the portal vein to the liver and through the liver to any other part of the body. The embryos form larval cysts (hydatid cysts) which are naturally most common in the liver and mesentery. The cyst consists of two layers. The outer layer or ectocyst is white and presents a characteristic laminated structure like the coats of an onion. The inner or germinal layer is granular and it is in this

material that fluid collects so that a cyst is formed. At various points along the germinal layer buds arise which become hollowed to form brood capsules in which little clusters of new scolices on stalks are produced. (Fig. 96.) Some of the buds develop into daughter cysts which become detached and float in the cavity of the mother cyst. From the lining of the daughter

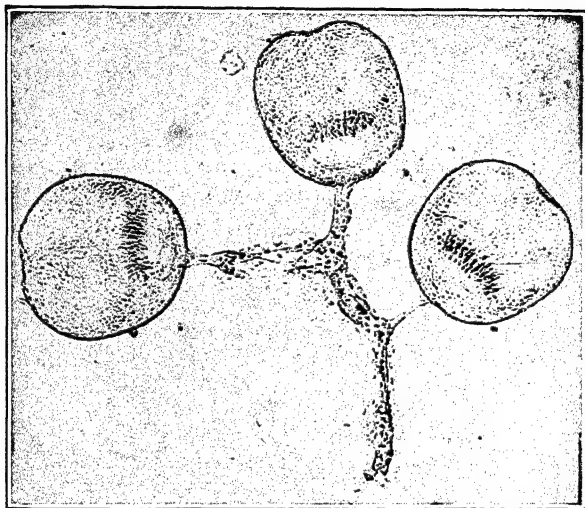


FIG. 96.—Stalked scolices of hydatid cyst showing hooklets.  $\times 200$ .

cyst new buds may arise which in turn produce new scolices. Each scolex is provided with 4 suckers and a crown of 30 to 50 hooklets. The scolex becomes invaginated into its own body in order to preserve the hooklets from injury, so that the suckers and hooklets face inward. (Fig. 98.) When the infected material (in the sheep or other intermediate host) is eaten by a dog the head is evaginated, and the scolices become attached to the intestinal wall by their hooklets and suckers, proceed to form proglottides, and develop into the mature worm.

The cysts may attain a great size and cause marked enlargement of the liver, form masses in the mesentery, etc. The fluid is clear and sterile, but contains a toxic substance



FIG. 97.—Echinococcus cyst of liver showing characteristic lining.

which may cause attacks of urticaria or produce toxic effects if the cysts are ruptured during removal. The blood may give a complement-fixation reaction against this substance. Intradermal injection of the fluid is said to give a specific reaction in cases of hydatid disease. Identification of the cysts is made by finding the characteristic hooklets, or by cutting sections of the wall and demonstrating the laminated structure of the ectocyst. (Fig. 99.)

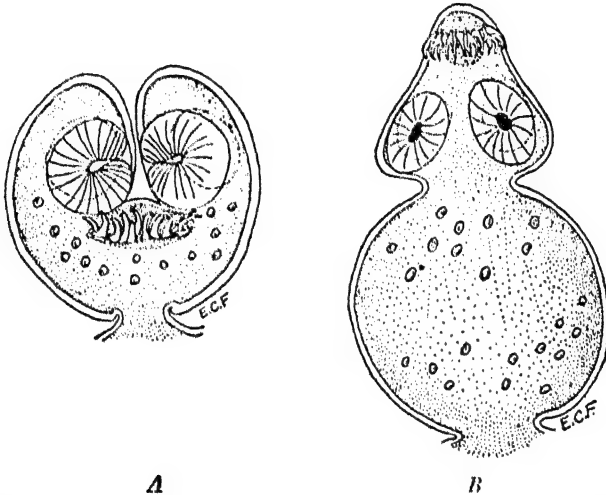


FIG. 98.—Scolex of hydatid cyst. *A*, Invaginated in cyst membrane; *B*, with evaginated hooklets and suckers.  $\times 400$ . (Faust.)

**ECHINOCOCCUS ALVEOLARIS.** There are two forms of echinococcus: *E. hydatidus*, which has just been described, and *E. alveolaris* or *multilocularis*, a much rarer form. The hydatid echinococcus forms large cysts filled with fluid, but the alveolar echinococcus cysts are entirely different, being extremely numerous, varying in size from the microscopic to that of a grain of seed or a pea, and containing gelatinous material but as a rule no scolices. They cause great enlargement of the liver, which at autopsy may be mistaken for mucoid carcinoma or congenital cystic liver. Necrosis may develop, with the formation of large ragged abscess cavities. The microscopic appearance may closely simulate tuberculosis with necrosis, epithelioid cells and giant cells. The disease is fairly common in Bavaria, Switzerland, and Russia, but is practically unknown in the great hydatid countries such as Australia, South America, and Iceland.

**Nematodes or Round Worms.**—A large variety of round worms may be parasitic for man both in tropical and temperate countries. Some of these are pathogenic, others are not. Only six will be considered here.

**ANKYLOSTOMA DUODENALE (UNCINARIA DUODENALIS).**—Ankylostomiasis or hookworm disease, like malaria, is one of the most prevalent diseases in the world. The Rockefeller Commission estimated that there were some 900,000,000 cases. The hookworm belt extends 'round the world on either side of the equator. The American variety of the worm is slightly different and is called *Necator americanus*. It is also found in temperate climates where the conditions are such that the soil is moist and warm as

in deep mines, in long tunnels, etc., so that hookworm disease is known locally as miners' anemia, tunnel disease, etc., and the skin manifestations are known as ground itch. The reason for all this will be apparent shortly.

The worm, as its name implies, lives in the upper part of the small intestine, although more in the jejunum than the duodenum. Large numbers, even hundreds, are found hanging firmly attached to the intestinal mucous membrane. It is said that as many as 10,000 have been found in one person. The worm is quite small, from 1 to 2 cm. in length, and is furnished with four teeth (*ankylos*, hooked), and a muscular esophagus by means of which the intestinal mucosa is drawn into the mouth. (Fig. 100.) The patient develops a profound anemia as the result of this heavy infection. This is due to the peculiar feeding habits of the hookworm, which draws blood

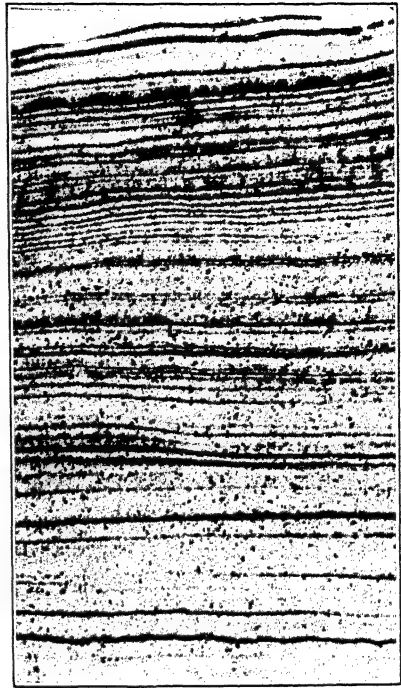


FIG. 99.—Laminated membrane of hydatid cyst.  $\times 200$ .



FIG. 100.—Section through human intestine, showing method of attachment of hookworm to the wall. (After Oudendal, in Transactions of Fifth Biennial Congress of Far Eastern Association, Courtesy of John Bale Sons & Danielsson, Ltd., London.)

from the mucosa of the bowel, pumps it through the alimentary tract, and forces it out from the anal orifice, a process which can be watched in the experimental animal. By means of such a mechanism 10,000 worms can soon remove a lot of blood. There is marked eosinophilia, a common manifestation of worm infections. The patient becomes weak, apathetic, and unable to work. There is marked evidence of anemia, including edema of the face.

The *mode of infection* provides one of those romances which makes the study of parasitology so interesting. The worms may live for six or seven years in the bowel, but they cannot multiply there. The eggs, of which 10,000,000 may be laid at one time, are passed in the feces, and if deposited



FIG. 101.—Hookworm larva (coiled) penetrating the skin. (Stumberg, Am. J. Hygiene.)



FIG. 102.—Hookworm dermatitis. (Dove, Am. J. Hygiene.)

in warm moist soil they develop into active embryos. These may be swallowed by another person, but the usual route is quite different and much more remarkable. In 1901 Looss, working in Egypt, showed that the hookworm sets forth on a veritable Odyssey in its effort to reach the small intestine. If wet mud containing the larvæ is rubbed on the skin a burning and itching is soon experienced, and by the time the mud is dry the active larvæ have disappeared through the skin leaving their own skins behind them. Looss followed their course in a leg about to be amputated. The larvæ are found to penetrate the hair follicle (Fig. 101), and from there they bore their way into the lymphatics by which they are carried to the venous blood stream or they may penetrate the veins directly. They are carried by the venous blood to the right heart and thence *via* the pulmonary artery to the lungs. When large numbers of larvæ enter the lungs it is common to find bronchitis and transient bronchopneumonia. In experiments on dogs it was found that the larvæ are filtered out of the circulation in the lungs, being unable to pass through the pulmonary capillaries. They burrow into the air vesicles, enter the bronchi, and crawl up the trachea. Having reached the glottis they climb over the epiglottis and

down the esophagus. The further passage through the stomach and into the duodenum is plain sailing. In the small intestine they develop into adult worms. How long the larvæ take to complete their Odyssey it is difficult to say, but as long as ten weeks has elapsed between the skin infection and the appearance of the eggs in the feces.

Ashford has added an important chapter to the story of the hookworm cycle by describing what he calls the larval stage of uncinariasis. He points out that the majority of the larvæ which penetrate the skin never reach the intestine, but die soon after invasion, as shown by the fact that the highest leucocytosis and eosinophilia occur at the beginning of the infection. Many other larvæ stray from the direct path and get hopelessly lost, remaining wanderers in the tissue until they perish. At the end of three months there is a second rise in the leucocyte count, due to the end of the natural term of life of the larvæ. During the larval stage there may be no adult worms in the bowel, but the patient suffers from marked lassitude, while his blood shows an eosinophilia. The latter, which may reach 60 per cent, appears to be due to disintegration of the larvæ and absorption of the foreign protein. Ashford's paper will be found extraordinarily interesting reading.

It is evident that coolies in coffee plantations, natives working in the mud on the banks of the Nile, miners in deep mines, tunnel-workers, etc., are peculiarly liable to the disease once the ground is heavily infected. The "ground itch," an eczematous skin eruption which affects those who walk in infected water with bare feet (Fig. 102) is merely an indication that the larvæ are invading the skin. When native workmen in hookworm areas are compelled to wear shoes the incidence of the disease shows a marked falling off. Proper disposal of excreta is another factor of prime importance in prevention of the disease. The diagnosis is made from the anemia, the eosinophilia and the presence of ova in the stools.

*ASCARIS LUMBRICOIDES*.—This is the common round worm which resembles the earthworm, being from 6 to 16 inches long, with tapering pointed ends and a pearly-white appearance. It is a common inhabitant of the small intestine, especially in children in whom it may produce reflex nervous disturbances; possibly a toxic element may also play a part. The worms, of which there are usually several, appear in the mouth. They lie free in the lumen of the bowel, and are not attached to the wall. Occasionally they are present in enormous numbers and may form masses which cause intestinal obstruction.

Although the ascaris is so different from the hookworm, yet parts of their life history are not dissimilar. Indeed, the behavior of the ascaris is even more strange. The ova develop into embryos in moist soil. The freshly passed eggs are not infective, and ten days or more must elapse before they are capable of causing infection. The capacity of the uterus has been estimated at about 27,000,000 eggs, and the average daily output for each female at 200,000. Infection is due to the ingestion of developing eggs on uncooked vegetables, etc. When the eggs are ingested they hatch into larvæ in the intestine. But here we come to the strange part. The larvæ are apparently unable to undergo complete development in the intestine until they have undertaken an extra-intestinal migration. They penetrate

the wall of the intestine and are carried to the right side of the heart either by the lymph and blood stream or by the mesenteric veins and inferior vena cava. They are filtered out by the lungs, and pass up the trachea and down the esophagus into the intestine just as in the case of the hook-worm. This strange migration occupies about ten days. In the intestine they develop into maturity if they have been derived from a human source, but not from the pig. In the latter case they are passed out of the body.

In the pig, on which animal most of the experimental observations have been made, large numbers of larvæ can be seen in sections of the lungs, as well as foci of hemorrhage and inflammation. In man the experimental ingestion of mature eggs has been followed in a few days by the development of the clinical picture of pneumonia. Koins swallowed approximately 2000 eggs; six days later he developed fever, chills, headache, malaise, rapid respirations, and a productive cough with the blood and larvæ (178 in one day) in the sputum. There was dullness over the chest and crackling râles. In clinical practice only a few eggs are likely to be taken at any one time, so that as a rule there are no physical signs. Ashford suggests that, as in ankylostomiasis, the larvæ may become lost and wander through the tissues, and that the presence of larvæ in the meninges may be responsible for the convulsions and nervous disorders in young children.

**OXYURIS VERMICULARIS (ENTEROBIUS VERMICULARIS).**—The thread worm or pin worm is a very common intestinal parasite, especially in children. It is only about 5 mm. long, and when passed in the stools resembles a motile piece of white thread. It lives in the lower part of the small intestine and the large intestine. The worms may pass out *per anum* and cause intense irritation and itching around the anus and in the vagina. A simple diagnostic method is to make a smear from the perianal region and examine it for ova, which adhere to the hairs in large numbers. In the bowel they usually cause no symptoms, but in weakly children they excite reflex nervous disturbances such as convulsions and enuresis. Masses of thread worms may occupy the lumen of the appendix. They may invade the mucosa and cause acute appendicitis. There is no intermediate host, and infection is direct from contaminated vegetables, fruit, etc. Massive reinfection may occur from the child's contaminated fingers.

**TRICHINA SPIRALIS (TRICHINELLA SPIRALIS).**—The disease trichiniasis is caused by a tiny round worm, the life history of which presents some very interesting features. It passes its complete life cycle in the body of one animal, but unless the host be eaten by another animal the embryos will all die. Surely a curious arrangement to have been evolved by a worm, but apparently a satisfactory one.

The parasite infects a variety of animals, in particular the rat, the pig, and man. Man becomes infected by eating the pig, and the pig is infected by eating the rat. Thus the life cycle is continued, but it comes to an end with man. Epidemics occur, particularly in Germany, from eating imperfectly cooked pork in sausages, etc. The embryos ingested in the infected pork develop into adult male and female worms in the intestine. These are very tiny, from 1 to 3 mm. long. After copulation the males die and the females burrow into the intestinal villi. The ova develop into embryos within the uterus of the worm, and the embryos are then discharged into the lymphatics. One female may discharge from 1000 to 1500 embryos in this way. The embryos enter the blood stream, and as their diameter is smaller than that of a red blood cell (6 microns broad though 100 microns long), they pass through the lungs and are carried to all parts of the body. During the stage of invasion they can be found in the blood if it is laked and in the cerebrospinal fluid. They are



actively motile, and penetrate the capillaries to invade the various organs. But they can only develop in the voluntary muscles and die out elsewhere, even in the heart. Every muscle in the body may be infected and yet the heart always escapes. Even it is probably infected at the beginning as indicated by the frequent presence of inflammatory foci, but the young embryos are apparently killed and disappear at an early stage.

Each embryo now enters a muscle fiber and undergoes partial development toward an adult worm, but full development is not possible unless the parasite finds itself in the digestive canal of another animal. The muscle fiber degenerates and loses its transverse striations. The embryos are found in the muscles as early as the ninth day after infection. They set up an acute myositis with infiltration of polymorphonuclears, eosinophils, lymphocytes, and giant cells. At first the long axis of the embryo is parallel to that of the muscle fiber, but by the end of the second week it becomes coiled up, encysted, and surrounds itself with a thick hyaline capsule. (Fig. 103.) Later this may become calcified. The encysted embryos are lemon-shaped, with the long axis in the direction of the muscle fibers. The embryos may remain alive for years awaiting the chance to complete their development in another animal. The life cycle is exactly the same in the pig. When the encysted embryos are swallowed by man the capsule is dissolved by the digestive juices, the embryos are liberated, and may attain maturity in a couple of days, when the whole process is repeated.



FIG. 103.—*Trichina spiralis* in muscle.  $\times 175$ .

It has been found that a dose of 15,000 r. filtered x-ray to meat infected with trichina larvæ will render it non-infective to the rat. This suggests a method of sterilizing commercial quantities of pork.

**Symptoms.**—The symptoms of trichiniasis occur during the period of invasion and are partly due to the irritation in the intestine, partly to the acute myositis. The muscles are hard and swollen and often extremely painful. Edema is usually present and is often marked in the face. Fever is a common symptom and may last for days or weeks. The severe cases are easily mistaken for typhoid fever, especially when there is diarrhea, but the leucocytes are increased in number and there is a marked and very characteristic eosinophilia, sometimes over 50 per cent. The eosinophilia usually disappears, but may persist for years. Convalescence sets in about the sixth week, but death may occur earlier from paralysis of the respiratory muscles. Many cases die in the early stage of the infection, apparently from the intense irritation in the wall of the intestine. The intradermal injection of a saline extract of trichina larvæ gives a positive reaction in about 90 per cent of cases after several weeks of infection. A positive reaction may still be obtained several years after the acute attack.

**TRICHURIS TRICHURIA.**—This worm, known as the whipworm, is one of the commonest intestinal parasites, living in the cecum and appendix, and sometimes

associated with acute appendicitis. The worm is only a few centimeters long. The posterior end of the male is coiled on itself, but most characteristic are the barrel-shaped eggs with a knob at each end (Fig. 104). The whipworms are attached only lightly to the intestinal mucosa and as a rule cause little or no disturbance to the unwitting host.

**FILARIA.** Filariasis is an infection by a nematode worm in which the adult worm lives in the lymphatics while the larvæ travel in the blood. It is a disease of tropical countries. There are several varieties of filaria, the most important being *Filaria bancrofti*, the larval or microfilarial form of which is known as *Filaria sanguinis hominis*. This parasite is of great historical interest, because it was in connection with it that Manson showed for the first time the part which the mosquito plays in the transmission of disease. It was Manson's work which suggested to Ross that malaria might also be conveyed by a mosquito, even though the infecting agents were so very different—the one a nematode worm, the other a protozoan parasite.

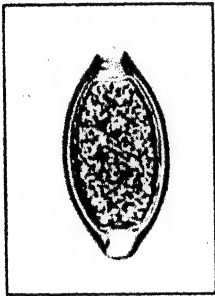


FIG. 104.—Egg of *trichuris trichuria*.  
(Kindness of Dr. J. C. Colbeck.)

The life history and habits of the filaria are remarkable even for an animal parasite. The adult worm lives in the lymphatics, especially those of the groin and pelvis. It is from 0.5 to 1 cm. in length and extremely thin. The male and female live together, and the ova develop in the uterus of the female into active larvæ. These are little eel-like bodies with a diameter no greater than that of a red blood corpuscle, so that they can pass through the smallest capillaries. Their most extraordinary characteristic is their periodicity, for they only appear in the peripheral circulation at night, hiding in the vessels of the lung and the large thoracic vessels during the

day. Their appearance synchronizes with the evening appearance of the mosquitoes, for they can only attain maturity in the body of that insect. One wonders how such an arrangement was first started. If the patient sleeps during the day and is kept awake during the night the larvæ are deceived and come out by day, so that the mosquitoes are disappointed. The larvæ do the patient no harm. This nocturnal periodicity may go on for years, the larvæ patiently awaiting the coming of the mosquito.

Lane points out that the usual explanation of filarial periodicity is not to be lightly accepted, for the hiding place of the larvæ by day has never been demonstrated, and it seems unlikely that they can maintain themselves in position in the large vessels of the thorax against the strong current of blood. He suggests that there may be a daily cyclical parturition by the females, and that the microfilariae perish rapidly. This view is supported by the observations of O'Connor who made serial sections of lymphatic tissue containing worms excised at operation. One extraordinary fact was brought to light. When the worms were removed before mid-day the turgid female was found to be crammed with microfilariae, but after 2 p.m. the females were collapsed and empty. All the living female worms from the same patient showed the same stage of development of the sex cycle. In a volunteer 720,000 microfilariae were injected into the blood stream; all were gone in the space of two hours. Destruction apparently takes place chiefly in the lymph nodes.

The *mosquito*, usually a member of the genus *Culex*, bites an infected person, and the larvæ pass with the blood into its stomach. They penetrate the stomach wall

and lodge in the thoracic muscles. Here they develop into young worms which make their way to the base of the proboscis and await injection into man, where sexual development may be attained and reproduction take place. The parasite is not actually injected by the mosquito but is deposited close to the hole in the skin made by the proboscis, and through this hole it penetrates the skin. It is said that the worms often pass out in pairs—probably male and female. They pass to the lymphatics, become mature, larvæ are liberated into the blood, and the cycle is complete.

*Pathological Effects.*—There may be none, though the patient may have larvæ in his blood for years. The adult worms are apt to produce *lymphatic obstruction*, especially if they are present in masses, and above all if they die and disintegrate. The obstruction causes varicosity of the superficial vessels and lymphatic edema. The regional lymph nodes are enlarged, their sinuses being distended with lymph.



FIG. 105.—Extreme degree of elephantiasis of scrotum in African negroes.

*Elephantiasis* may develop. This is a condition in which the tissues become enormously thickened and indurated. The legs and scrotum are the parts commonly affected. (Fig. 105.) It is probable that lymphatic obstruction alone will not give rise to elephantiasis, but that infection and lymphangitis must be superadded. The abdominal lymphatics may rupture, especially if there is obstruction of the thoracic duct, and lymph escapes into the peritoneal cavity giving *chylous ascites*. If the renal or vesical lymphatics are obstructed there may be *chyluria*. The patient may show small subcutaneous nodules not necessarily associated with edema. These represent an inflammatory reaction around a coiled-up worm. I have seen such a nodule removed from the arm under the impression that it was a thrombosed vein. (Fig. 106.)

*DRACUNCULUS MEDINENSIS (Filaria Medinensis, Guinea-worm).*—This parasite of tropical countries, commonly known as the guinea-worm, is surpassed by none of its relatives in peculiarity of behavior. As usual the male is insignificant, but the female is long and very thin; the average length is 50 to 80 cm., but it may reach  $1\frac{1}{2}$  meters. The intestinal canal is atrophic and the anus absent, but the uterus, crowded with larvæ, runs almost the entire length of the worm. The larvæ have to be discharged into water, and the female finds the necessary water with a certainty

which a water-diviner might envy. The worm works its way through the tissues until it reaches a surface. As the natives go bare-footed, the worm usually makes its appearance on the sole of the foot, but it appears in the upper extremities of Europeans, where water is more often in contact with the hands and arms, and on the backs of water-carriers whose water-skin is slung over that part. The passage down the leg may take as much as eighteen months. The head of the worm pierces the surface with the formation of a small blister, and when water is poured on the skin enormous numbers of larvae are discharged from the greatly distended uterus so that the fluid becomes milky. The larvae are taken up by a fresh-water crustacean belonging to the genus *Cyclops*, in which they pass through a necessary stage of development before being ingested by man. It is for this reason that the worm has to make for water, however long the journey may be.

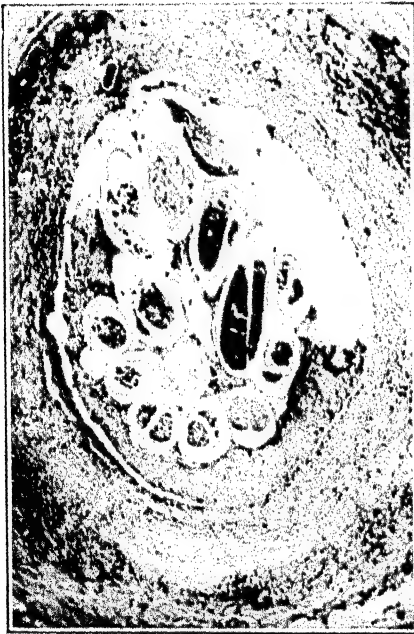


FIG. 106.—*Filaria* in a small vessel.  $\times 40$ .



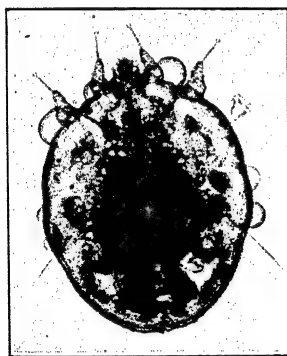
FIG. 107.—*Dracuncul* worm partially removed from a ruptured eschar of the fourth toe. (After Castellani and Chalmers, *Tropical Medicine*.)

If the worm dies or if the larvae are liberated into the tissues as the result of injudicious attempts at removal, there may be severe inflammation and abscess formation. The natives have an ingenious method of persuading the worm to leave its habitat. They pour water on the foot, and in the resulting effort of parturition the worm is induced to emerge on the surface. The protruding part is wound round a small stick and the treatment is repeated at intervals, the stick being given an additional twist on each occasion. By this simple means as the result of patience and perseverance the worm can finally be completely removed. (Fig. 107.) It has been suggested that these worms were the "fiery serpents" which afflicted the Children of Israel in the migration from Egypt, and that Moses was the first in history to demonstrate the classical method of removal by winding the "serpent" on a rod, gradually drawing it out. He made a model in brass of the procedure.

## EXTERNAL PARASITES: ARTHROPODS

Some of the more common of these will be merely mentioned. For detailed description the reader is referred to works on skin diseases and parasitology. A few of the external parasites are of importance not only because of the irritation they produce but because of the much more serious diseases which they may be the means of carrying. The commonest skin parasites are "itch insect" causing scabies, lice and fleas.

**ACARUS SCABIEI.**—The "itch insect" which causes scabies is shaped like a turtle and is about 0.5 mm. long (Fig. 108). The impregnated female bores a tunnel into the skin, laying her eggs at the end of the tunnel where the young are hatched. These in turn bore new tunnels. The male remains quietly on the surface and causes no trouble. The symptoms of scabies depend on the irritation produced by the burrowing female. The burrows take the form of curved dark lines, and are most common between the fingers, at the wrists, in the axillæ, etc. Vesicles may form at the entrance to the burrows and these are often infected by the scratching induced by the intense itching.

FIG. 108.—*Acarus scabiei*.  $\times 75$ .FIG. 109.—*Pediculus capitis*.  $\times 30$ .

**PEDICULI.**—A variety of pediculi or lice may infest the body. *Pediculus capitis*, the head louse, lies on the scalp. (Fig. 109.) The ova or "nits" are minute white bodies which can be seen attached to the hairs. They hatch out in about a week. *P. corporis*, the body louse, lives on the surface of the skin and breeds in the clothing. By its bites it causes great irritation of the skin, and the itching causes scratching with subsequent infection. The body louse is responsible for carrying the infection of typhus fever, relapsing fever, and trench fever. It does this in the same way as the mosquito, *i. e.*, by biting first a sick man and then a healthy person. *P. pubis* is found especially in the pubic region.

**FLEAS.**—*Pulex irritans* is the common flea, a wingless insect 2 to 4 mm. long. *P. cheopis*, the rat flea, is of importance because it conveys plague not only from one rat to another but also from rat to man.

**FLIES.**—The body tissues or cavities may be infected with the larvæ (maggots) of certain flies, a condition known as *myiasis*. The eggs may be laid in the nasal cavities, wounds, etc., where they develop into maggots. One type of larva tunnels

about in the skin, causing the condition called "creeping eruption." This condition may, however, be produced in other ways. In the southern United States probably the commonest cause is the larva of *Ancylostoma braziliense*.

### ADDITIONAL READING

- Ascaris.** KOINO: Japan Med. World, 1922, **2**, 317.  
**Bilharzia Hematobia.** SHAW AND GHAREEB: J. Path. and Bact., 1938, **46**, 401.  
**Cysticercosis and Epilepsy.** MACARTHUR: Trans. Roy. Soc. Trop. Med. and Hyg., 1934, **27**, 343.  
**Diphyllobothrium Latum.** BIRKELAND: Medicine, 1932, **11**, 1.  
**Filaria.** LANE: Lancet, 1933, **2**, 399. O'CONNOR AND HULSE: Lancet, 1933, **2**, 404.  
**General References.** ASH AND SEITZ: Pathology of Tropical Diseases; an Atlas, Philadelphia, 1945. BEVITT AND DICKSON: A Text-book of General Pathology, London, 1926 (Chapter VI). BLACKLOCK AND SOUTHWELL: A Guide to Human Parasitology for Medical Practitioners, 4th ed., 1940. FAUST: Human Helminthology, Philadelphia, 1939. MANSON-BAHR: Manson's Tropical Diseases, 10th ed., Baltimore, 1936. THOMPSON AND ROBERTSON: Protozoology, London, 1929.  
**Histoplasmosis.** AMOLSCHE AND WAX: Am. J. Path., 1939, **15**, 477. DARLING: J. A. M. A., 1906, **46**, 1283. HENDERSON, *et al.*: J. A. M. A., 1942, **118**, 885. MELENY: Am. J. Trop. Med., 1940, **20**, 603. PARSONS: Arch. Path., 1942, **34**, 229. PARSONS AND ZARAFONETIS: Arch. Int. Med., 1945, **75**, 1. WRIGHT AND HACHTEL: Ann. Int. Med., 1944, **15**, 309.  
**Hookworm.** ASHFORD, *et al.*: J. A. M. A., 1933, **101**, 843.  
**Intestinal Protozoa.** DOBELL AND O'CONNOR: The Intestinal Protozoa of Man, London, 1921. LYNCH: J. Lab. and Clin. Med., 1932, **17**, 661; Protozoan Parasitism of the Alimentary Tract, New York, 1930.  
**Malaria.** American Association for the Advancement of Science. A Symposium on Human Malaria. Washington, D. C., 1941, Pt. 6. GREAVES: Canad. Med. Assn. J., 1946, **54**, 568.  
**Protozoa.** FAUST: J. Lab. and Clin. Med., 1932, **17**, 639.  
**Taenia Echinococcus.** DEW: Hydatid Disease, Sydney, 1928. JAMES AND BOYD: Canad. Med. Assn. J., 1937, **36**, 354.  
**Toxoplasmosis.** PINKERTON AND WEINMAN: Arch. Path., 1940, **30**, 374. WOLF, *et al.*: Am. J. Path., 1939, **15**, 657. ZUELZER: Arch. Path., 1944, **38**, 1.  
**Trichina Spiralis.** Gould *et al.*: Am. J. Path., 1953, **29**, 323. WELLER AND SHAW: Trans. Assn. Am. Phys., 1932, **47**, 41.

## Chapter

# 9

## GROWTH AND ITS DISORDERS

GROWTH is the most fundamental of all physiological functions. It is brought about by multiplication of cells, not by increase in their size. There is little difference in size between the cells of a mouse and the cells of an elephant; the difference is one of number. In the same way the cells of a cancer may be actually smaller than those of the tissue from which it arises. The cells of any given species of animal have a strictly limited power of multiplication. When this limit is reached the growth of the animal ceases. This it is which determines the size of animals, so that all members of one species are of approximately the same size, no matter how the external conditions may vary. To this rule the fish offer an exception, for the members of a species, such as trout, may greatly increase in size when placed in a more suitable environment. Growth is brought about by the change of non-living into living material. All dead matter is potentially living, and we see the transformation of dead into living matter going on ceaselessly. "The molecules of the dead world are waiting to be delivered from the bonds of death," as Lorrain Smith remarks in a delightful monograph which should be consulted by anyone interested in the subject of growth. He points out that theoretically the whole inorganic substance of the material world might be converted into living substance by the substance already living.

Cells not only grow (multiply); they also differentiate. Now differentiation and growth are mutually antagonistic, and this is a profound biological principle. Differentiation depends on environment. Unless cells are compelled by their environment to differentiate they will feed, grow and multiply forever without doing any work, thus resembling human beings. Division and function are not possible at the same time. The more highly differentiated a cell becomes, the more does it lose its power of reproduction, and therefore its ability to give rise to tumor formation; this is seen in the case of striated muscle, nerve cells, red blood cells, etc. Cancer cells fail to differentiate; instead they continue to grow. As Lorrain Smith says, they do not fall into the normal procession. They fall out. They do not keep step; the procession is moving slowly and they move fast.

### **METAPLASIA**

Metaplasia is the transformation of one type of tissue into another type. This process has definite limits. An epiblastic tissue can only produce another epiblastic tissue, mesoblast can only produce mesoblast. Metaplasia is best seen in the closely-related connective tissues, as when cartilage is

converted into bone. *Anaplasia*, or reversionary atrophy, must not be confused with true metaplasia. Anaplasia is merely the reversion of a more highly to a less highly differentiated form.

**Epithelial Metaplasia.** True metaplasia occurs in response to a call for altered function or at least as the result of altered environment. If the prolapsed uterus becomes everted the columnar epithelium is changed into a squamous stratified form better fitted to withstand friction. As the result of continued irritation, *e. g.*, from gall stones, the columnar epithelium of the gall-bladder may also become squamous, and from this altered epithelium a squamous-cell carcinoma may arise. The bronchial epithelium in a bronchiectatic cavity may undergo the same change and come to resemble the epidermis. (Fig. 110.) The more highly specialized glandular

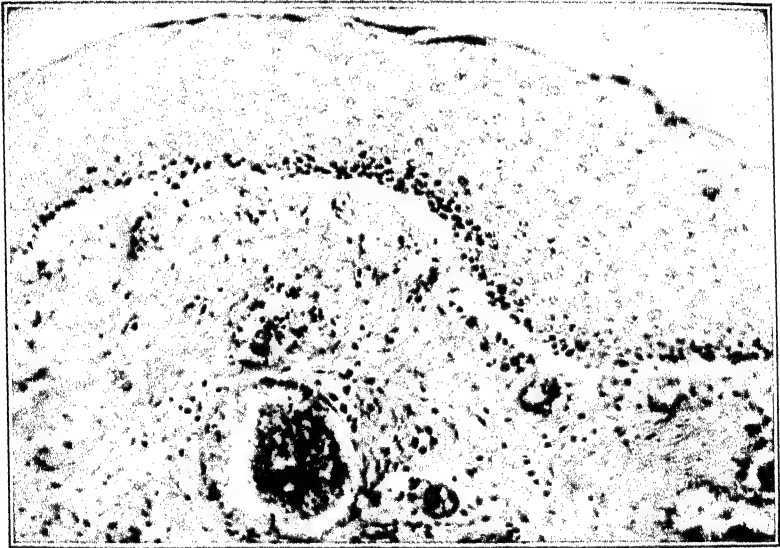


FIG. 110. - Remarkable metaplasia of epithelium lining a bronchiectatic cavity. The single layer of columnar cells is converted into typical stratified squamous epithelium.  $\times 150$ .

epithelia (liver, kidney, etc.) appear to be incapable of true metaplasia.

**Connective-tissue Metaplasia.**—Examples of this are of common occurrence. Fibrous tissue, myxomatous tissue, cartilage, and bone are all closely related, and one may become changed into the other. The commonest change is that of cartilage into bone. In old age ossification of the laryngeal and tracheal cartilages is common enough. This is certainly not due to altered function, but may be connected with altered environment. Bone may be formed in the walls of degenerated arteries the seat of arteriosclerosis, or in an eye which is destroyed and functionless. It may be encountered in the edges of a wound in the abdominal wall. Apparently the connective-tissue cells become converted into bone-forming cells. In myositis ossificans bone is formed in the voluntary muscles and may replace



them to a large extent; this bone is probably formed from the connective tissue between the muscle fibers. Many examples of metaplasia are seen in connective-tissue tumors; thus the cells of an osteogenic sarcoma of bone may form fibrous tissue, mucoid tissue, cartilage or bone.

**Endothelial Metaplasia.**—When serosal endothelium such as that lining the pleura or peritoneum is irritated either experimentally or by disease it may undergo marked metaplastic changes. In place of being flattened it may become cubical, columnar, or even stratified. The cubical and columnar cells may surround spaces so as to give a glandular appearance.

## ATROPHY

Atrophy is a diminution in size, a shrinking of cells or fibers which have reached their full development. Hypoplasia indicates a failure of full development. Atrophy may occur under a great variety of different conditions. Some of the most important of these are old age, lack of nourishment, disuse, the action of toxins, pressure and interference with nerve supply. As *age* advances there is a general tendency towards atrophy, best seen in the uterus, ovary, breast, lymphoid tissue, and bone-marrow. Chronic *starvation* causes wasting of adipose tissue and muscles; atrophy also follows decreased blood supply due to arteriosclerosis. *Disuse* of a structure results in atrophy, as is seen in the anterior horn of the spinal cord after amputation of a limb. *Pressure* atrophy is seen in the erosion of bone by an aneurism or the atrophy of liver cells in amyloid disease. *Neurotrophic* atrophy is due to loss of trophic impulses when a motor nerve is injured, but it is difficult to be sure how much of this is due to disuse.

## HYPERTROPHY AND HYPERPLASIA

**Hypertrophy.**—Hypertrophy is an increase in the size of individual cells or fibers as a result of which the organ may become enlarged. Enlargement of an organ from any other cause should not be called hypertrophy. There is no increase in the number of the individual elements; such an increase is covered by the term *hyperplasia*. True hypertrophy never occurs as the result of irritation, but always in response to some demand for increased function. It is convenient to recognize three varieties of hypertrophy—physiological, adaptive, and compensatory—although the dividing lines cannot be drawn too sharply.

**PHYSIOLOGICAL HYPERTROPHY.**—Physiological hypertrophy occurs apart altogether from disease. The best example is the pregnant uterus. At the end of pregnancy the muscle fibers are ten times as long and four times as broad as in the non-pregnant uterus. The hypertrophy of muscles which follows hard work (the blacksmith's arm) may be placed in this group or in the next.

**ADAPTIVE HYPERTROPHY.**—Adaptive hypertrophy is best seen in hollow muscular organs when the outlet is partially obstructed. The wall of the organ becomes thickened owing to an increase in the size of the muscle fibers. As examples may be mentioned the left ventricle in stenosis of the

aortic valve or high blood-pressure with its increased peripheral resistance (Fig. 112), the stomach in pyloric obstruction, the bowel in chronic intestinal obstruction, and the bladder in stricture of the urethra. The hypertrophy of voluntary muscle as the result of exercise may be placed in this group or in the preceding one.



FIG. 111.—Compensatory hypertrophy of one kidney.

**COMPENSATORY HYPERTROPHY.**—Compensatory hypertrophy is an increase in size to compensate for loss of tissue. It is best seen in paired organs. When one kidney is removed or atrophies because of disease the remaining kidney does the work of the two and becomes correspondingly enlarged. (Fig. 111.) There is no formation of new elements, but merely an increase in the size of the existing tubules and glomeruli. When a portion of the liver or thyroid is removed the organ is restored to its original size, a process often spoken of as compensatory hypertrophy, but this is a hyperplasia rather than a hypertrophy.

**Hyperplasia.**—By hyperplasia is meant an increase in the number of the cells of a part. Its limits are more shadowy than those of hypertrophy, and



FIG. 112.—Concentric hypertrophy of the left ventricle in aortic stenosis.

it gradually merges into the process of neoplasia or tumor formation. Hyperplasia, unlike hypertrophy, is often the result of irritation, although it may also be compensatory or adaptive. Lymphoid tissue readily undergoes hyperplasia as the result of local irritation. Compensatory hyperplasia is seen in the bone-marrow which so readily becomes hyperplastic when there is a demand for more blood. When a portion of the thyroid gland is removed the remaining tissue undergoes marked hyperplasia so as to compensate for the loss. The liver also has remarkable powers of compensatory hyperplasia.

## MALFORMATIONS

The subject of malformations, maldevelopment, and monsters is an extremely large one, involving as it does a study of all the possible errors which may occur during the complex process of development. The scope of this work, not to mention the lack of knowledge of the writer, makes any attempt to cover the subject out of the question. All that will be attempted will be to give a catalogue of the principal conditions, so that the student will at least become familiar with their names. If he wishes to enquire into the rationale of the various malformations he may consult Adami's *Principles of Pathology*, or the monographs by Ballantyne and Schwalbe. For convenience the subject may be divided into: (1) maldevelopments, inclusions, etc.; (2) local malformation; (3) double monsters.

**MALDEVELOPMENTS.**—Many minor errors of development are compatible with life and even with health. Most of these will be described when diseases of the individual organs are discussed. There may be too few digits or too many (supernumerary). Two or more of the fingers or toes may be fused together, a condition of *syndactyly*. The kidneys may be fused at the upper or the lower pole, the horse-shoe kidney. Remnants of fetal structures which normally disappear may remain, *e. g.*, Meckel's diverticulum, Wolffian ducts, thyroglossal duct, ductus arteriosus, etc. The congenital anomalies of the heart form a subject in itself. In the course of development portions of an organ may become detached and included in another organ. Thus inclusions or "rests" of adrenal cortex may be found in the kidney and the pelvic organs, pancreatic tissue occurs in the wall of the stomach and duodenum, thyroid tissue at the base of the tongue and elsewhere in the neck. This displacement of tissue is called *heterotopia*. Along the normal lines of closure of developmental clefts dermal tissues may be infolded and included in the underlying structures. The included tissue may start to grow, forming an *inclusion dermoid*. There lesions are commonest in the face and the middle line of the body both anteriorly and posteriorly. It is possible that certain tumors of mixed structure (parotid and kidney tumors) may arise from these inclusions.

**LOCAL MALFORMATIONS.**—During normal development a number of grooves and fissures must be accurately closed. If any of these remain open either wholly or in part grave malformations may result. These may be reviewed briefly.

**Neural Groove.**—The entire groove may remain open, but usually the deficiency is only partial. If the cranial part is open the condition is called *cranioschisis*; if the spinal part is unclosed it is called *rhachioschisis*. In *cranioschisis* the brain may be absent save for an amorphous mass of tissue on the floor of the cranial cavity, a condition of *anencephaly* or *acrania*; the child is an *anencephalic monster*. The frontal part of the cranium may be closed, while the occipital part remains open and the brain hangs out at the back. When the patency is more limited in extent there may merely be some prolapse of the meninges or the brain covered by skin—*meningocele* or *encephalocele*. In the spinal canal by far the commonest defect is

*spina bifida*, the lowest part of the canal remaining unclosed. Here also there may be meningocele or meningomyelocele.

*Sternal Fissure.* If the patency is at all marked extra-uterine life is impossible, for the lungs are unable to expand. The heart may protrude through the opening, a condition of *ectopia cordis*.

*Abdominal Fissure.* The two halves of the abdominal wall may fail to close. There will then be evisceration or protrusion of the viscera.

*Urogenital Fissure.* The bladder may be extruded or it itself may fail to close, a condition of *ectopia vesicae*. If the urethra does not close it is represented by a groove on the dorsal surface of the penis or clitoris, a condition of *epispadias*.

*Facial Clefts.* If there is gross failure of the various facial clefts to close, the fetus will be a monster. Very much commoner is *hardlip* and the often associated *cleft palate*. The maxillary process fails to unite with the intermaxillary bone and the defect may be limited to the lip or may extend back into the hard and even the soft palate. The lesion may be unilateral or bilateral. If the intermaxillary bone is absent there will be a median cleft palate.

*Branchial Clefts.* The branchial clefts below the first (which forms the Eustachian tube) may remain open. The third is the most frequently involved. The entire cleft may remain open, constituting a *branchial fistula* which connects the pharynx with the skin surface of the neck. The outer end may remain open; this is a *branchial sinus*. The commonest lesion is a *branchial cyst*, in which both ends are closed, but the intermediate portion remains open.

*Rectal Malformations.* There may be a *persistent cloaca*, in which the rectum fails to be separated from the external genitalia. If partial separation occurs a *fistula* is formed, the rectum communicating by a passage with vagina, bladder or urethra. The septum which separates the skin from the hind gut may not be broken down as normally occurs; this is a condition of *imperforate anus*.

**DOUBLE MONSTERS.** Monsters may be single or double. Instances of single monsters have already been given, although of course it is not always easy to say when a defect is sufficiently severe to justify the use of the word monster. One form has not yet been mentioned. The two eyes may be fused so that there is a single eye in the center of the forehead. The condition is known as *cyclops*, named of course after Polyphemus in the *Odyssey*. Double monsters are an anomaly of twin formation. They may be symmetrical or asymmetrical.

*Symmetrical Monsters.* In these, two individuals are joined together. The union may be in the head region, in the thoracic region, or in the sacral region. (1) *Craniopagus* is fusion in the head region. The fusion often only involves the scalp and cranium. There may be two faces looking in opposite directions. Or there may be a single head, the two bodies remaining separate. The position may be reversed, the bodies being fused into one, while the heads remain separate. There is then a two-headed monster or *dicephalus*. (2) *Thoracopagus* is fusion in the thoracic region, the remainder of the two bodies remaining separate. There may be a common thoracic cavity with a double set of viscera. Sometimes there is only union between the ensiform cartilages and the surrounding soft parts. Such a condition is quite compatible with life, and it was in this way that the Siamese twins who lived to the age of sixty-three years were united. (3) *Ischiopagus* is fusion in the pelvic region. The head, thorax, and spinal column of each individual remain separate, but there is union below the umbilicus and a pelvic ring in common. In the above description only the main types of symmetrical double monsters have been mentioned. There are endless variations.

*Asymmetrical Monsters.*—1. *Unequal Twins.*—As a rule, both twins develop equally. But one may die and be converted into an amorphous lump of flesh. In other cases the fetus is fairly well developed, but the heart is poorly developed or rudimentary. This is an *acardiac fetus*. In such cases the course of the circulation

has been reversed; the acardiac fetus is nourished by the blood of the other twin, so that the heart, having little to do, does not develop.

2. *Parasitic Fetus*.—This is an example of a double monster in which the development of one of the twins is arrested. This twin does not die as in the case of unequal twins, because it is united with the other twin upon which it lives as a parasite. The parasite may be attached in the cranial, thoracic, or pelvic region, giving a *parasitic craniopagus*, *parasitic thoracopagus*, or *parasitic ischiopagus*. The parasite may be fairly well developed or may be a mere jumble of tissues. When such a rudimentary mass is attached to the mandible it is called an *epignathus*. It may be attached to the sacrum, forming a *sacral teratoma*.

3. *Congenital Teratomata*.—As already indicated, the parasitic mass may be unrecognizable as a separate individual, consisting merely of a confused mass of tissues such as brain, bone, cartilage, teeth, skin, hair, and glands. This may be attached to the exterior of the body, most often in the sacral region, or it may be included in the body cavity (mediastinum, ovary, testicle, etc.). These are congenital teratomata or dermoids, so-called because they contain dermal structures. They are to be distinguished from the teratomata which develop in adult life, usually in the ovary, more rarely in the testicle, and which are probably derived from segregation of one of the blastomeres of the developing ovum.

#### ADDITIONAL READING

**Growth.** БОУД: Canad. Med. Assn. J., 1934, 31, 124. СМИТН: Growth, Edinburgh, 1932.

## Chapter

# 10

## TUMORS

### THE GENERAL PATHOLOGY OF TUMORS

No single sentence definition of a tumor can be satisfactory, because it leaves too many loopholes, but for most purposes a tumor or neoplasm may be defined as a local growth of new cells which proliferate without control and which serve no useful function.

Tumors can be divided into two great groups: the benign, or innocent, and the malignant. In typical and fully developed cases the distinction can be made at a glance. Unfortunately there are intermediate forms in which the differentiation may be extremely difficult, and a benign tumor may develop into a malignant one. All malignant tumors are included under the common heading of cancer, meaning a crab, for claw-like processes characterize both the tumor and the animal. Malignant tumors of epithelium are called carcinoma, those of connective tissue are termed sarcoma.

The features which distinguish a benign from a malignant tumor are easy to enumerate, but unfortunately with experience exceptions to nearly all of these will suggest themselves. As the most important of all the many duties of the pathologist is to differentiate between benign and malignant tumors, it will be realized that his task may prove to be one of great difficulty.

### CHARACTERISTICS OF MALIGNANCY

In deciding the all-important question of the malignancy of a tumor it is necessary to consider both the *histology*, that is to say the arrangement of the tumor cells and their relation to the surrounding normal tissue, and the *cytology*, that is to say the character of the tumor cells and especially the character of their nucleus and nucleolus.

1. **Infiltration.**—A malignant tumor infiltrates the surrounding tissue. It sends claws into it like a crab. An innocent tumor grows by expansion like a balloon, and is usually separated from surrounding structures by a capsule of compressed tissue. But a benign glioma blends imperceptibly with its surroundings, and an angioma infiltrates without being malignant. Conversely, a malignant tumor in its initial stage may be a non-invasive carcinoma or carcinoma in situ.

2. **Recurrence.**—This clinical term indicates that the tumor has reappeared after removal or radiotherapy. It does not mean that a new tumor has originated, but rather that some of the cancer cells have escaped injury

and have multiplied to form another mass. Cancer cells may remain dormant for many years and then begin to grow again. The proof of this fact will be seen when the question of the spread of tumors is considered. There is always the possibility of the development of another tumor. Thus a cancer of the lip may be removed completely, but a second cancer may arise in another part of the lip some years later.

**3. Rapidity of Growth.**—Rapid growth is characteristic of malignant in contrast to benign tumors, but to this there are many exceptions. Some cancers, especially in old people, are of very slow growth. If a benign tumor should start to grow quickly it should arouse suspicion of a malignant change. The presence of numerous *mitotic figures* is suggestive of malignancy. The more rapid the growth, the more numerous the mitoses. The nucleus may be represented by a dark mass of chromatin, or the chromatin may be collected as a bar across the center of the cell (monaster,

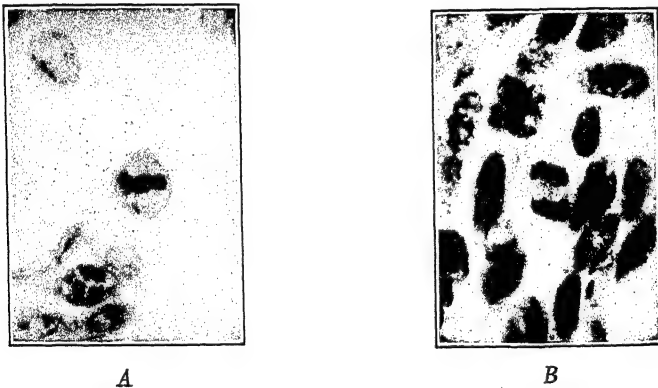


FIG. 113.—Mitotic figures. A, shows the monaster stage (metaphase) and B, the diaster stage (anaphase).  $\times 700$ .

metaphase) (Fig. 113A) or in two separate masses, one at each pole (diaster, anaphase) (Fig. 113B). In malignant tumors atypical mitosis (multi-centric division) may sometimes be seen (Fig. 114). Colchicine has a remarkable power of arresting the completion of cell division, so that great numbers of mitotic figures may be seen. As it is during mitotic division that the cell is most readily damaged by radiations, it is evident that the use of colchicine may find a place in the radiotherapy of cancer. It must be remembered that mitosis is present in granulation tissue and in other rapidly regenerating cells (Fig. 49, page 109), so that it is no proof of malignancy.

**4. Nuclear Changes.**—The reproduction of a cell is governed by the nucleus, and in particular by the nucleoproteins of the chromatin. Ultra-violet spectroscopy shows that there is intense activity of this mechanism in cancer cells. For this reason the pathologist pays special attention to the nucleus in determining the question of malignancy of a tumor. The nucleus of a cancer cell is likely to be large and hyperchromatic, so that it

stains intensely with hematoxylin, or the chromatin network may be coarse. The nucleus varies much in size and shape, and the cells themselves show similar variation. The nucleolus is large in proportion to the size of the nucleus, an important feature which may be more evident in frozen sections of the unfixed tissue or in wet films. (Fig. 116) Microincineration shows an increased inorganic content of the nucleus.

5. **Anaplasia.** A malignant tumor fails to reproduce the structure of the tissue from which it grows, whereas an innocent tumor may reproduce it perfectly. This lack of differentiation is called anaplasia, a concept first introduced by Hansenmann in 1893. The more anaplastic the tumor, the more malignant is it likely to be. When the cells fail to show a normal relationship to their neighbours they are said to show *loss of polarity*.



FIG. 114.—Atypical mitosis. The chromosomes have divided into three groups in the center. Three centrosomes and attraction spheres are also seen.  $\times 1500$ .



FIG. 115.—Smear of cancer of breast showing irregular cells and large nucleus and nucleolus.  $\times 500$ .

The *grading of tumors* as regards degree of malignancy depends mainly on loss of differentiation, coupled with such features as hyperchromatism and the number of mitotic figures. On this basis it has become the practice to divide some of the carcinomas into four groups according to their microscopic appearance, group 1 being the most differentiated and benign, grade 4 the most anaplastic and malignant (Broders). Epidermoid carcinoma (Figs. 116-119) and adenocarcinoma (Figs. 120-123) are the types of cancer which lend themselves best to grading. The chief value of grading is that it serves to indicate those cases (grades 3 and 4) which may be expected to respond well to radiotherapy. The method has severe limitations, and generalizations based on it are dangerous, for a tumor may not show a uniform structure, and some parts may be much more differentiated than others, so that a biopsy may be misleading. The clinician must not take grading too seriously in determining the prognosis of a malignant tumor,





FIG. 116, Grade 1.

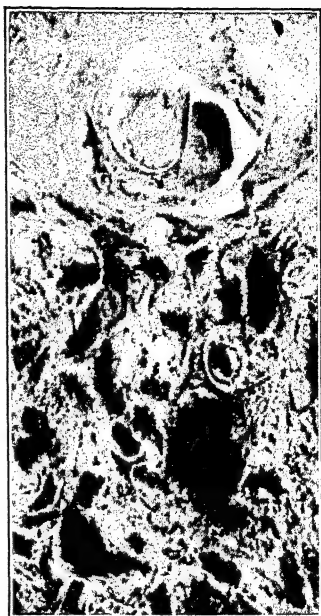


FIG. 117, Grade 2.

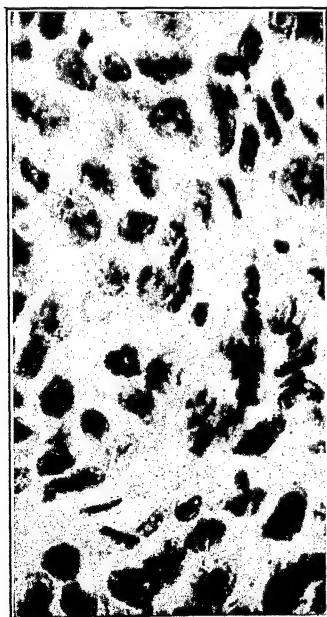


FIG. 118, Grade 3.

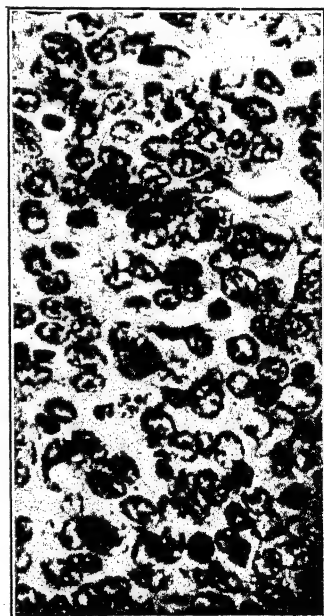


FIG. 119, Grade 4.

FIGS. 116 TO 119.—The four grades of epidermoid carcinoma. Differentiation is complete in Fig. 116; Fig. 119 is extremely anaplastic with many mitotic figures. Fig. 116,  $\times 200$ ; Figs. 117 to 119,  $\times 500$ .

but must consider the age of the patient, the extent of the disease, its duration, its rate of growth, and, most important of all, involvement of the regional lymph nodes.

6. **Loss of Polarity.** Epithelial cells which are arranged in sheets show a regular polarity, by which is meant the arrangement of the cells with

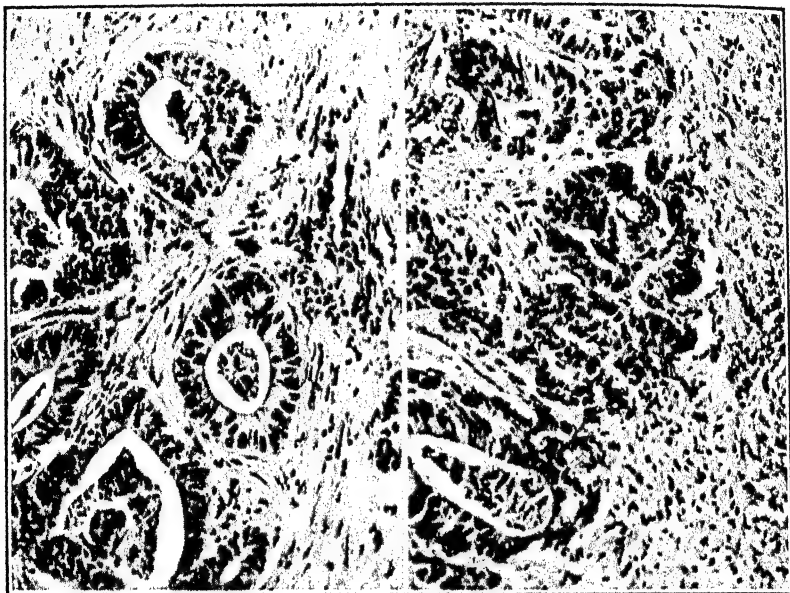


FIG. 120, Grade 1.

FIG. 121, Grade 2.

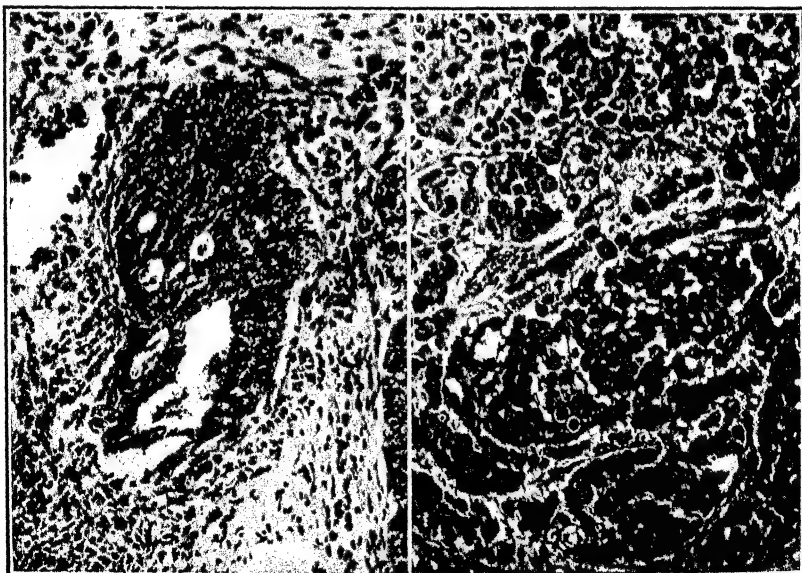


FIG. 122, Grade 3.

FIG. 123, Grade 4.

FIGS. 120 to 123.—The four grades of adenocarcinoma.  $\times 125$ .

their long axis perpendicular to the surface of the sheet. One of the early signs of a malignant change is loss of the normal polarity, so that the cells now present what may be termed a jumbled arrangement in relation to the surface.

**7. Spread to a Distance.**—A malignant growth sooner or later sets up secondary growths or metastases in the lymph nodes which drain the part and in distant organs. Even here there are exceptions, for malignant gliomas do not behave in this way.

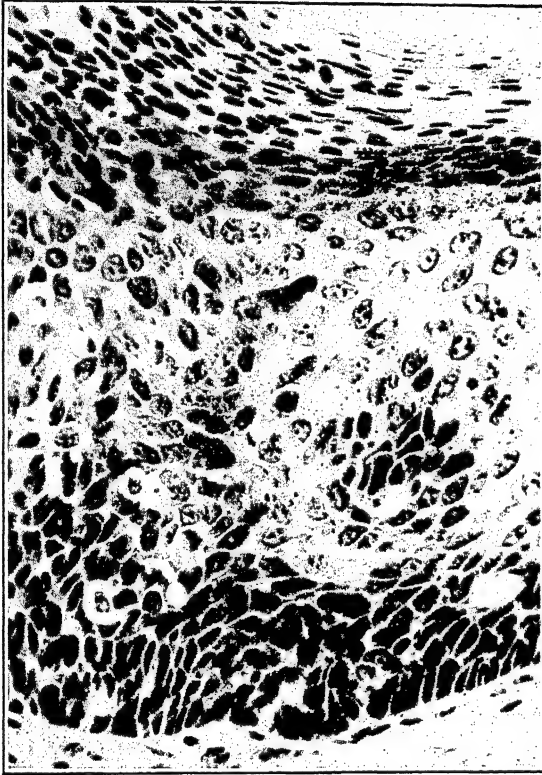


FIG. 124.—Preinvasive carcinoma (carcinoma in situ) of the skin. Note the hyperchromatic nuclei, jumbled arrangement of the cells (loss of polarity), mitoses, and impression of restlessness. There is lack of keratinization in the stratum corneum with abnormal preservation of nuclei.  $\times 375$ .

**8. Fatal Outcome.**—A malignant tumor, as its name implies, tends to kill the patient wherever it grows, even in the hand or foot. An innocent tumor will only cause death if it happens to grow in a vital organ.

*Preinvasive Carcinoma.*—An important step in the fight against cancer is the recognition by the pathologist of the very earliest beginnings of the malignant process. When metastases have occurred it is too late. When invasion of the deeper tissues can be recognized it may be too late. But when the malignant change is still cytological rather than histological the disease is curable. This state of affairs is known as *carcinoma in situ* or

preinvasive carcinoma. The three cytological features which indicate this condition are nuclear changes, anaplasia, and loss of cellular polarity (Fig. 124). The picture at once strikes the observer as being atypical and bizarre. The cells appear to be becoming restless. This ominous change is not necessarily confined to one spot. Carcinoma, whether preinvasive or invasive, may have what has been described as a *wide field of origin*. Reference to Figure 125, will show a multiple origin in a limited space. The foci of origin, however, may be widely separated. This is best seen in Paget's disease of the breast where preinvasive carcinoma of the skin of the nipple is associated with foci of carcinoma of the ducts of the breast, sometimes localized, at other times distributed over a wide area. It is in carcinoma of the cervix uteri that recognition of preinvasive carcinoma is of the greatest practical importance.

### METHODS OF SPREAD

The ability to spread, both locally and to a distance, is one of the most important characteristics of a malignant tumor, for it is the main stumbling block to the successful treatment of cancer. The power and method of



FIG. 125. -Multiple foci of independent growth in a rodent ulcer.  $\times 45$ .

spread constitute the main feature of the natural history of the tumor, and this may provide a valuable clue to correct diagnosis not only to the clinician but to the pathologist. When at autopsy tumors are present in the lung and the adrenal, it is not necessary to look down the microscope in order to determine which of these is the primary growth. It is only necessary to know the age of the patient. In a child the primary tumor is a neuroblastoma of the adrenal medulla; in an adult it is a carcinoma of the lung. The answer to this riddle will be found in the discussion on tumors of the lung and adrenal. The secondary growths or metastases may dominate the clinical picture. Thus a patient may present himself with all the symptoms of a cerebral tumor, and only a slight cough which he may forget to mention will suggest to the well-informed physician that the case is one of cancer of the lung with metastases in the brain and that treatment is useless.

PLATE V



Tumor Emboli in Bloodvessels in Wall of Intestine.

We have learned much about the routes of tumor spread. We know next to nothing about the conditions which determine this spread. Some cancers spread by one route, some by another, some spread from the very beginning, some do not spread to a distance for many years.

There are six methods by which a tumor may spread: (1) by infiltration, (2) by lymphatics, (3) by bloodvessels, (4) along natural passages, (5) through serous cavities, (6) by inoculation.

1. **Infiltration.**—The fact that cancer cells, both carcinoma and sarcoma, may penetrate the surrounding tissues is everyday knowledge. Indeed it represents the very essence of malignancy and forms the most important distinguishing feature between benign and malignant neoplasms.

Yet it is difficult to form a mental picture of the mechanism of this infiltration. Cancer cells lack the mobility of polymorphonuclear leucocytes and macrophages, and they are faced with the resistance of the mucopolysaccharides of the ground substance. It is possible that this barrier may be broken down by enzyme action, for at least some malignant cells seem to have the power to produce hyaluronidase.



FIG. 126.—Tumor embolus in a blood vessel.  
× 375.

**Lymph Spread.**—Tumor cells can readily enter lymphatic channels. They may extend along these channels by *permeation* (Fig. 149, page 266), or they may be carried both to regional and distant lymph nodes by *lymphatic embolism*. The tumor cells are at first confined to the peripheral subcapsular lymph sinuses. There is little direct spread from node to node, but spread readily occurs by anastomosing lymphatics. The lymphatic spread of carcinoma is primarily embolic, the nodes where the emboli lodge preventing further spread until the node is completely overwhelmed. Marked hyperplasia of the reticuloendothelial cells lining the sinusoids (sinus histiocytosis) may occur in the regional nodes apart from the presence of metastases, and this, at least in cancer of the breast, indicates a favourable prognosis (Black *et al.*).

All the lymph from the abdominal organs reaches the thoracic duct, which finally opens into the left jugular vein. Spread along the thoracic duct explains those cases in which cancer of the gastrointestinal tract is



Fig. 127. Tumor invading wall of vein via a lymphatic and surrounded by a thrombus.  
The darker material is the tumor.  $\times 70$ .



Fig. 128.—The same tumor failing to penetrate wall of artery.  $\times 325$ .

associated with pulmonary metastases whilst the liver remains clear. Involvement of the supraclavicular nodes on the left side of the neck is occasionally due to massive growth of tumor throughout the length of the duct, but usually to tumor emboli from the cisterna chyli lodging behind the valves at the termination of the duct, with extension along the lymphatics to the nodes.

**3. Blood Spread.**—Cancer cells may reach the blood either by way of the thoracic duct or by direct invasion of the bloodvessels. The veins are invaded with great readiness, but the arteries very rarely. The chief reason for this striking difference appears to be the fact that lymphatics frequently penetrate the walls of the larger veins and form a plexus reaching to the sub-endothelial region; this is not true of the arteries. (Figs. 127 and 128). A thrombus forms over the eroded endothelium, and this is invaded by tumor cells. It is this combination of thrombus and tumor which becomes detached and forms the tumor emboli that are likely to result in metastases. Clumps of tumor cells unconnected with thrombus may form pure emboli, but they may not give rise to metastases owing to inability to become colonized at the site of impaction.

The site of metastases is governed largely although not entirely by the anatomical distribution of bloodvessels, especially veins. Cancers of organs drained by the portal circulation will metastasize for the most part to the liver. Cancers of the kidney, uterus and limbs, parts drained by the systemic veins, metastasize as a rule to the lungs.

Unfortunately it not infrequently happens that tumors do not behave according to rule and metastases occur in unexpected places. A few illustrations will suffice.

Bone metastases are so common in cancer of the prostate that they often dominate the clinical picture. The secondary growths are in the spine and particularly in the lumbar region. This distribution is explained by the *vertebral system of veins* (Batson), which pass up inside the spinal canal and anastomose with sacral, lumbar, abdominal and thoracic veins, as well as with veins penetrating the vertebral bodies and cranial bones. There are frequent reversals of flow in this vast intercommunicating system the result of coughing, straining and increase of intra-abdominal pressure, for these veins are without valves. During these reversals a pathway up and down the spine exists which does not involve the heart and lungs, a system which is more a lagoon with occasional ebb and flow than a channel of streaming blood. Flow takes place into the system during coughing, serving to explain the high incidence of cerebral metastases in cancer of the lung and of cerebral abscess secondary to lung abscess.

At autopsy it often happens that the liver contains an incredible number of metastases such as are never found in the kidney or spleen. This is not due to the fact that the liver provides a specially favourable soil for the growth of tumor cells, but because the *branches of the portal vein*, readily invaded by tumor, have an arterial distribution and become smaller as they proceed. It is in this way that secondary tumors can give rise to tertiary ones, and these new tumors can again repeat the process.

The *pulmonary veins* provide another method of dissemination. Not only a primary bronchogenic carcinoma but also metastatic growths in the



lung may penetrate the wall of a pulmonary vein and thus reach the left side of the heart and the systemic circulation. It can be shown experimentally that tumor cells readily traverse the pulmonary capillaries, but it is tumor emboli rather than individual tumor cells which set up metastases. The filter of the lung is likely to hold up emboli, so that the lungs share with the liver pride of place as regards frequency of secondary growths. Tumor emboli, however, are not synonymous with metastases. Tumor emboli in the lungs often die out, as M. B. Schmidt showed many years ago. They become coated with fibrin, the cells are not properly implanted, and fail to develop into tumors. It is the embolus composed partly of the tumor and partly of thrombus which is likely to grow when it becomes impacted in a vessel.

**4. Spread by Natural Passages.**—Tumor cells may be carried along such passages as the bronchus, bowel and ureter, and it is conceivable that they might become implanted on an epithelial surface and form a new growth. This might explain the simultaneous occurrence of the same type of tumor in the renal pelvis and the bladder. It is more probable, however, that the cells have passed down lymphatics in the wall of the tube, or that two independent tumors have developed at the same time.

**5. Spread Through Serous Cavities.** This method, known as transcolonic spread, is the explanation given for the frequent transfer of cancer cells from the stomach to the ovaries, rectal serosa, etc. Small implantations on the peritoneum can often be traced between stomach and ovary. There is nothing inherently improbable about this concept, but to the writer the arguments in favor of spread along lymphatics carry greater weight. One place where the passive transfer and implantation of tumor cells can be accepted without reserve is the cranial cavity, where there are no lymphatics. Malignant glial tumors shed cells into the ventricles and subarachnoid space, throughout which they may be carried by the cerebrospinal fluid and form multiple secondary growths.

**6. Inoculation.** Every surgeon knows the possible danger of transferring tumor cells by inoculation into the surrounding tissue in the course of an operation for cancer. Instruments and gloves which may have become contaminated by cutting into the tumor to obtain tissue for a biopsy are not used again. Even the basin of water in which the surgeon dips his gloved hands may carry the cells, which can be seen in a centrifuged specimen. In one case a carcinoma of the breast was removed and a skin flap was taken from the thigh to close the large gap. A few months later a nodule having the same structure as the breast cancer developed in the scar in the thigh. Everything had been changed between the two incisions with the exception of the contents of the basin which contaminated the fresh gloves. (Brandes *et al.*)

**Distribution of Metastases.**—From what has been said about methods of spread the reader may think that the spread of tumors is well understood. This is far from the case. Every week the pathologist in a large hospital encounters examples which he cannot explain. Three carcinomas of the stomach seem alike in every respect, yet the first will remain localized apart from involvement of a few regional lymph nodes, in the second case the liver may be riddled with tumors, whilst in the third the liver may

escape but the brain and other viscera may be the site of metastases. Endless examples could be given. There is certainly no relation between the size of the primary tumor and the occurrence of metastases. Nor is there any necessary relation between the number of tumor emboli and the number of metastases. Others as well as myself have observed the occasional case where the viscera are filled with innumerable emboli but secondary growths have not developed. The fate of the emboli may depend on chemical and metabolic factors. The soil must be considered as well as the seed, a truth which is self-evident in the case of transplanted tumors in the experimental animal.

The immunity of skeletal muscle to metastases is remarkable. And yet when a suspension of carcinoma cells is injected into the femoral artery of an animal there is massive involvement of the muscles of the leg (Eisenberg). Injection of the same material into the femoral vein results in massive tumors only in the lungs. Malignant gliomas spread only by infiltration and implantation; they do not metastasize. This is probably due to non-invasion of the bloodvessels and to lack of any connection between the perivascular lymph spaces and extra-cranial lymphatics, because when gliomas are implanted intraperitoneally or into subcutaneous tissue they grow rapidly (Zimmermann).

Tumor emboli may develop quickly, as in the liver, or they may die out, as in the muscles, or they may remain after removal of the primary tumor and only begin to multiply many years later. The best example of a prolonged latent period is that of melanoma of the eye; metastases may develop in the liver twenty years after the primary tumor has been removed.

## THE CAUSES OF CANCER

The problem of cancer has long been shrouded in a traditional veil of mystery. Indeed that word occurs in the very first sentence in the discussion on the etiology of cancer in previous editions of this book. C. P. Rhoads remarks that it has been viewed as a problem that can be solved only by the providential disclosure of some secret of nature as yet unknown. To this may be added the words of Peyton Rous: "The tumor problem is the last stronghold of metaphysics in medicine. But it is a stronghold closely besieged." There is a clue to the mystery of cancer, though it is a clue which nature guards very jealously.

One of the chief stumbling blocks in the way of a proper concept of neoplasia and its causation is the idea that cancer is a disease entity like tuberculosis. It is rather a group of diseases like the infectious fevers with multiple etiology. Still better, it is a disease process like inflammation. The inflammatory process may be caused by a wide variety of agents (irritants) such as streptococci, a foreign body, radium and allergy. So also the neoplastic process may be caused by a wide variety of agents (carcinogens), which may be physical, chemical, viral and hormonal. We cannot explain the exact mechanism by which an irritant such as a foreign body causes inflammation, nor can we explain the exact mechanism by which a carcinogen such as methylcholanthrene causes cancer, but we can hazard a guess.

Cancer is abnormal cell growth and cell division, so that a study of its causation involves a consideration of this process in the normal cell. In the normal cell reproduction by cell division goes on for a limited period and then ceases, whereas in a malignant cell the process goes on continuously. This is the essence of malignancy. The real mystery is why normal growth stops, not why malignant growth is continuous. The power of the normal cell to divide is not lost. At any time the process, now known as repair, may recommence under the stimulus of chemical substances released as the result of cell injury. Some cells, such as those of the bone-marrow and epidermis, multiply continuously throughout life.

The living cell is a seething mass of activity, not the static structure we see under the microscope. This activity is regulated by a multitude of enzymes, and when the cell divides the same enzymes are present in each daughter cell. The cell is acted on by various external influences and also by hormones. As a result of this action a change may take place in one of the regulating enzymes. This physical defect, which is represented physiologically by lack of control, will be transmitted to the daughter cells. There is now uncontrolled growth without reference to the needs of the organism.

The enzymes, which are self-perpetuating proteins that regulate all phases of cell activity including reproduction, appear to be identical with the genes, those band-like structures which are distributed along the chromosomal threads. For each enzyme in the cell's metabolism there is one gene in the chromosomes. The genes are most easily seen in the giant chromosomes of the salivary gland of the fruit fly, *Drosophila*, where they number from 5,000 to 10,000. The cells of the salivary gland in this and other two-winged flies have 1,000 times the volume of ordinary cells. Chromosomes are extremely fine threads of nucleoprotein, which during mitosis become wound into tight spirals that resemble rods, but which uncoil after cell division. It is these rod-like structures, not the fine chromosomal threads, which are seen by the pathologist in mitotic division.

Growth is a nucleoprotein business which is completely dependant on the self-duplicating property of the genes and is regulated by the genes. The master control lies with nucleic acid, which is conjugated with proteins to form nucleoproteins. The nucleoproteins possess the unique property of self-duplication, and are the only substances in the body which can do this and do it endlessly. Viruses as well as genes are nucleoproteins, and both are distinguished by the power of self-duplication.

Nucleic acid consists of giant molecules, each with thousands of smaller molecules or nucleotides, and each of the nucleotides is made up of a nitrogenous base, linked with a sugar and phosphoric acid. There are four kinds of nucleotide, each with a different nitrogenous base. The nitrogenous base consists of one of two purines and one of two pyrimidines. The sugar is of two varieties, ribose and deoxyribose. There are therefore two types of nucleic acid (and nucleoproteins), ribonucleic acid or RNA and deoxyribonucleic acid or DNA. These are present in all living cells, but they function in different parts of the cell, DNA being confined to the chromosomal threads of the nucleus, whilst RNA occurs in the cytoplasm and the nucleolus. The genes are particles of DNA. Both types of nucleoprotein stain with basic dyes, but they can be distinguished and their distribution in the cell demonstrated by two very different techniques, the Feulgen reaction and selective light absorption. The Feulgen reaction gives an intense purple with DNA, but is negative with RNA. Both forms of nucleic acid absorb ultraviolet light of a wave length which does not affect proteins. Microspectrophotometry with ultraviolet light has been a potent weapon for the investigation of the nucleoproteins, especially in the hands of Caspersson.

The foregoing considerations provide the basis for a concept of the possible nature of the neoplastic process. Cancer is in essence a change in cell metabolism. That such a change has occurred is indicated by the high

rate of aerobic and anaerobic glycolysis with the production of large amounts of lactic acid (Warburg). The cancer cell does not appear to need oxygen, deriving its energy from glycolysis. Cultures of fibroblasts develop into sarcoma when grown under partial anerobic conditions by repeated exposure to an atmosphere of nitrogen (Goldblatt and Cameron). The regulator of the complex machinery of intracellular enzymal activity, the governor of the engine, is nucleic acid with its conjugated proteins. There are grounds for belief that there is a difference between the anabolic process for the nucleic acid of the chromosomes in the normal cell and the cancer cell. We know that radiations can produce a permanent change in a gene by damaging the chromosomes. If a radiation strikes one atom of a molecule under the right conditions it will knock electrons out of it, producing a physical change in that atom and a chemical change in the molecule. A virus, which like an enzyme is a self-perpetuating nucleoprotein, can produce tumors by disrupting the normal regulatory mechanism. Genes are linked together in the chromosomes, members of a community working for the common good. A virus, which perhaps began as a gene, is a detached solitary particle, an outlaw or lone wolf, essentially antisocial in its effect, a parasite living on the wealth accumulated by the genes. Gene mutations may give the cell the power of greater reproduction and make it insensitive to normal inhibitory influences.

The infinitely intricate and delicately balanced regulating mechanism of chromosomal genes and enzymes which controls metabolism and cellular reproduction can be upset in various ways. The interference may lead to permanent changes or mutations in the genes. If these mutations are sufficiently serious they may be lethal and the cell will die. If the change is such as to permanently speed up the mitotic rate the result will be cancer.

A mechanism needs replacement of material and parts, whether it be living or non-living. Likewise the self-perpetuating chromosomal nucleic acid must renew its parts, *i. e.*, the two purines and pyrimidines, the desoxyribose and the phosphoric acid. By tagging a molecule of one of the purines such as adenine, which is done by replacing an atom of nitrogen or carbon with its radioactive isotope, it is possible to follow the replacement of essential material in the nucleoprotein of the chromosomes. This is facilitated by speeding up the mitotic rate as can be done by removing two-thirds of a rat's liver with resulting active hyperplasia of the remainder.

Knowledge that the regulatory mechanism of a cell can be tampered with offers a potent weapon for research both in the production and the control of malignant neoplasia. Just as the regulator of a watch may be moved to fast or slow, so may the mitotic rate be permanently accelerated by carcinogens or retarded by radiation and colchicine. As one cell will produce 60,000 daughter cells after sixteen divisions, it is apparent that even a slight increase in the rate and rhythm of cell division will soon produce a tumor. It is possible to prepare a synthetic substitute for the purine adenine, 2, 6-diaminopurine, which the cell will accept but which it will find poisonous instead of nutritious. This technique has already proved successful in the control of transplanted animal tumors in tissue cultures of malignant tumors, both animal and human.

Cancer can be produced experimentally in animals or it may occur spontaneously in man and in animals. Human cancer may be due to known

exogenous agents such as radiation, in some cases an endogenous agent such as a hormone may be presumed to be a causal factor, whilst in the great majority of cases there is no apparent cause, although we can be certain that some carcinogen is responsible. In our present state of ignorance it seems justifiable to picture carcinogens, whether of external or internal origin, as agents which tamper with the composition of the nucleic acid regulatory mechanism, producing a self-perpetuating and therefore permanent derangement.

There is, of course, no one cause of cancer, just as there is no one cause of inflammation. Inflammation signifies a flame, a fire, but cancer is also a fire which burns continuously. There are many methods of starting a fire, some physical, some chemical. So also must there be many methods of starting different kinds of cancer and cancer of different organs. Moreover, a fire does not necessarily start at one spot; a match may be applied in several different places. This is true also of cancer. There is no need to think of it starting in one cell; it may originate in a number of adjoining areas. This is known as the wide field of origin, and is well illustrated in Figure 125.

**Exogenous Carcinogens.** Carcinogens acting on the body from without may be chemical, physical or viral in nature. Clinical evidence may point to the influence of environment, even though no definite agent can be incriminated.

The first observation on *chemical carcinogenic agents* was that of Sir Percival Pott in 1775, who noticed that cancer of the skin was especially common in men who worked with tar and he offered the suggestion that the tar acted in some manner as a causal agent. This may be linked with the observation that cancer of the lip is especially common among fishermen on the west coast of Scotland, who, in mending their nets, put the bone needle threaded with tarred twine between their lips. In 1915, that is to say one hundred and forty years after Pott's paper, Yamagiwa in Japan put this idea to the test by painting tar on a rabbit's ear every day for six months, and succeeded in producing cancer of the skin. This was an epoch-making discovery, because for the first time it was possible to produce a malignant tumor at will. Subsequent work has shown the mouse to be a much more suitable animal than the rabbit.

Tar is a highly complex substance containing a great variety of chemical agents. The next step was to determine the active agent or agents present in tar which were responsible for producing the cancer. This step was taken by Kennaway and Cook in 1932, when they succeeded in isolating the hydrocarbon benzpyrene from tar and showed that it possessed a high degree of carcinogenic activity. It was then noticed that benzpyrene gave a spectrum with fluorescent light very similar to that of a group of recently synthesized hydrocarbons, of which one of the important members is 1:2:5:6 dibenzanthracene. On following up this lead it was at once found that the latter substance was powerfully carcinogenic, and as it had the advantage of being a chemically pure substance of known composition, it has become the most popular agent in the experimental production of cancer. It is interesting to note that 1:2 benzanthracene has practically no carcinogenic activity, but the attachment of a new benzene ring in the

5:6 position gives it great carcinogenic power. A very slight change in the chemical structure of a substance may convert it from a non-carcinogenic into a carcinogenic agent. Methylcholanthrene is another actively carcinogenic hydrocarbon which deserves mention because it is an artificial compound prepared from cholic acid, an organic substance occurring *naturally* in the body, thus suggesting the possibility of an endogenous chemical carcinogen.

Any of these agents can produce either carcinoma or sarcoma at the site of application. If applied to an epithelial surface carcinoma develops, if injected subcutaneously sarcoma is the result. By this means it has been possible to produce carcinoma of the skin, kidney, liver, testis, bladder, and uterus, as well as sarcoma of the subcutaneous tissue and peritoneum. Brain tumors (gliomas) can be produced by the intracerebral implantation of pellets of methylcholanthrene. When fibroblasts from the rat or mouse are grown in tissue culture in a medium containing a powerful carcinogenic chemical, such as methylcholanthrene, they are changed into cells which are similar to the cells in cultures of sarcoma induced by injection of the carcinogen into subcutaneous tissue (Earle and Voegtlin).

A carcinogenic agent of extraordinary potency was discovered by accident in the course of testing the toxicity of a new insecticide, acetyl acetaminofluorine. This substance when implanted in the tissues causes neither inflammation nor tumors, but when given by mouth to rats it produces cancer of the liver, pancreas, breast, bladder, lung and salivary glands, as well as sarcoma and leukemias (Bielschowsky).

Murray and Woglom have demonstrated the interesting fact that a tissue may apparently be malignant before any structural change can be detected. They tarred a mouse for four months; at the end of that period the skin showed no change. The epithelium was then removed and transplanted into another animal, and typical carcinoma developed.

When we turn to cancer in man we find much evidence in support of known external carcinogens, some of which are chemical and others physical.

Workers who come in contact with tar products, oils and petroleum are liable to develop skin cancer. Aniline dye workers get cancer of the bladder. The active agent is beta naphthylamine, which causes cancer of the bladder in the dog as well as in man, but not in the mouse and rat, because the metabolic product excreted in the urine by the latter is non-carcinogenic. This illustrates one of the pitfalls of experimental cancer work, because what may be harmless for man may be carcinogenic for the animal and vice versa. Other carcinogens which might be either chemical or physical are the chotta and the kangri. The chotta is a cigar which is smoked in southern India with the lighted end in the mouth. Addicts have a high incidence of cancer of the mouth. The natives of Kashmir wear a hot basket of charcoal, the kangri, under their clothes for purposes of warmth, and cancer of the abdominal wall is common among them, whereas it is almost unknown amongst other races. Some authorities believe that statistical evidence shows that heavy cigarette smoking bears a causal connection to cancer of the lung. Circumcision seems to prevent the development of cancer of the penis, by eliminating an accumulation of oily smegma under the foreskin which apparently acts as a carcinogen.

Of the *physical carcinogens* the most striking are radiations in their various forms. Whole body radiation to the rat is a potent carcinogenic agent (Koletsky and Gustafson). Even a single dose of 660 r is followed by a wide variety of benign and malignant tumors of the skin, connective tissue and viscera in nearly half the animals, the malignant tumors being about evenly divided between sarcoma and carcinoma. The early workers with x-ray developed cancer of the skin of the hand after many years. Leukemia, a malignant condition of the blood-forming organs, is an occupational disease of radiologists. Radium produces the same effect. Girls in Newark, New Jersey, who painted the dials of watches with luminous radioactive paint developed bone sarcoma owing to the deposit of radioactive material in the bones. Anyone who is continually exposed to radiations, whether he be a shoe salesman or a dweller near an atomic pile, is in danger of radiation cancer. As mankind is crossing the threshold into the atomic age, there is need for awareness of fresh dangers. It is possible that radiations may act by producing chemical changes with the formation of hydroxyl radicals from decomposition of water with depolymerization of the nucleic acid molecule and resultant chromosomal damage. The miners in Schneeberg and Joachimsthal for centuries have suffered from a high incidence of cancer of the lung; this is now known to be due to radioactive uranium. Actinic light radiation is also carcinogenic, thus explaining the high incidence of cancer of the skin and lip amongst the white population of the tropics and the southern United States. This form of cancer is very rare in the negro, who is protected by the high melanin content of his skin.

In many forms of cancer although the causal agent is not known there is reason to believe that it is related to environment or occupation and therefore should be classed as an external carcinogen. The truth is that throughout life we swim in a sea of carcinogens, and it is more by good fortune than good management that some of us escape to die from other causes.

The incidence of different forms of cancer varies greatly in different countries and in different parts of the same country. This suggests the action of an environmental agent. Thus cancer of the liver, a rare disease in most countries, is very common in Java and amongst the Bantus of South Africa. This may be due to a deficiency in some element of diet, a negative agent (see below). What has been called the social grading of cancer, *i. e.*, variations in incidence with different economic levels, is observed particularly in those organs which might be exposed to an external carcinogen (Fig. 129). This grading is very marked in the alimentary canal, but only above the pylorus. Cancer of the cervix in women and of the lung in men is much more prevalent amongst the poorer classes in Copenhagen (Clemmeson). The Survey of Cancer in London, published by the British Empire Cancer Campaign in 1952, shows a significant excess of cancer of the lip and mouth in general and dock laborers, of cancer of the pharynx and esophagus in publicans and barmen, of cancer of the skin in workers in chemicals, pitch and tar, of cancer of the larynx in singers, actors and clergymen. The incidence of cancer of the stomach varies greatly in different countries. In Honolulu, which by reason of its isolation and its mixture of races may be regarded as a human laboratory for the study of cancer, gastric cancer is far more common amongst the Japanese

than amongst the general population. Some of the differences in the sex incidence of cancer may really be due to differences in occupation and environment; cancer of the lung is seven times more common in men and cancer of the esophagus ten times more common.

*Trauma* is often accused of being an exogenous carcinogenic agent, nearly always falsely. No tumor has ever been produced experimentally by a single trauma, even in animals with a high cancer incidence. Sarcoma of bone is often traced back to an antecedent trauma, but if such a causal relationship exists it is strange that the innumerable fractures of bone are never followed by sarcoma. In compensation cases a true history of trauma preceding the appearance of a tumor is often forthcoming. This can be explained in two ways. (1) The trauma, by causing pain and bruising, draws attention to the presence of a tumor (in the breast, etc.) previously unnoticed. Hemorrhage into the tumor may cause it to swell quickly, and this may be followed by more rapid growth. (2) Coincidence, seeing that both injury and tumors are so common. The possibility that a traumatic lesion might form the starting point of cancer cannot be denied, but the fact that the vast majority of traumatic cancers are Workmen's Compensation cases gives food for thought. Special monographs have been devoted to this difficult subject.

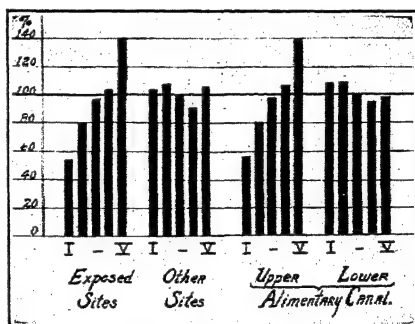


FIG. 129.—Cancer mortality by social classes. (Registrar-General's Decennial Suppl. England and Wales, 1921.)

*Viruses* are external carcinogens for certain animal tumors, mostly in birds. As a virus is a mass of self-propagating nucleoprotein, which resembles the genes so closely and whose habitat is the interior of the cell, this seems only natural. It was in 1910 that Peyton Rous first showed that a cell-free filtrate of a fowl sarcoma could produce a new tumor when inoculated into another fowl. The active agent has the characteristics of a virus. Similar agents have been found in many other mesenchymal tumors of birds, in an adenocarcinoma of the kidney in the frog (Lucké), and in a papilloma of the skin in the wild cotton-tail rabbit (Shope). This is a benign tumor, but when the virus is injected into the domestic rabbit a more aggressive tumor is produced which presently develops into a true cancer. When this stage is reached the active agent can no longer be obtained from the malignant lesion, with the cells of which it seems to have become incorporated.

Rous points out that carcinogenic viruses differ from chemical carcinogens in a number of ways. (1) The viruses are specific in their action, each producing only one type of growth. No known chemical carcinogen produces only one kind of tumor. (2) Multiplication of the virus is coterminal with the growth of the tumor it produces, whereas the chemical



carcinogen initiates the growth, but may then be removed without affecting the continued growth of the tumor. (3) The chemical carcinogens produce tumors in a wide variety of animals, whereas the viruses only produce tumors in the species of animal from which they have originally been isolated.

Bittner's work on the *transmissible milk factor* in breast cancer in mice has opened a new chapter in experimental cancer research. It is well known that it is possible to breed a strain of mice with a high incidence of cancer or a strain with no tendency to that disease. This was naturally regarded as an example of hereditary transmission of the disease due to a change in the germ plasm. Bittner, however, found that when newborn mice of a high cancer strain were fostered by mothers of a low cancer strain the tumor incidence was greatly reduced. Conversely newborn mice of a low strain when fostered by mothers of a high strain showed an increased incidence of breast cancer. The factor responsible is evidently extra-chromosomal in character, one transmitted in the milk which can be isolated and is believed to be a virus. The infected females may or may not become cancerous, depending probably on the presence or absence of conditioning factors, but in either case they transfer the agent in the milk to the progeny, and it can be recovered from the mammary tumor should one develop. It is now known that the male also can transmit the virus, probably in the sperm. The bearing of this work on the possibility of a human mother with a family history of breast cancer transmitting it to her baby in her milk has not yet been determined.

**Endogenous Carcinogens.** The best examples of this group are the sex hormones, but it is possible that other hormones and other organic compounds formed in the body as the result of disordered metabolism may act as carcinogens. Thus the carcinogenic sterol methylcholanthrene can be produced by the chemist from cholic acid of the bile by a series of processes which might well occur in the body. The basic structure of the sex hormones, the chemical carcinogenic hydrocarbons, and such sterols as cholesterol is fundamentally the same, all of them possessing the condensed-carbon-ring skeleton known as the phenanthrene nucleus.

*Estrin* acts on the mammary epithelium, which is normally under the influence of ovarian stimulation. Lacassagne has shown that if estrin is injected from birth onwards into a strain of mice which have a natural tendency to develop mammary cancer the incidence of that tumor is very greatly increased, and even in male mice of the same strain mammary cancer can be produced. It is important to note that in a non-cancerous strain the hormone is powerless to produce cancer. Removal of the ovaries in mice of a high cancer strain will prevent the occurrence of spontaneous mammary cancer. These facts suggest the possibility that the hormone may be a conditioning factor, a co-carcinogen, rather than the essential carcinogen itself. Mice can be protected against the Bittner milk factor if the ovaries are removed in early life so that the breast tissue does not develop.

It is probable that the *male sex hormone* plays some part in the genesis of cancer of the prostate. If the testes are removed in early life the prostate fails to develop. In a case of cancer of the prostate both the primary tumor

and the secondary growths show marked restraint of growth as the result of castration or the administration of estrin which inhibits the action of androgen.

**Dietary Factors.**—Very little is known about this subject, but one or two factors may be significant. When dimethylaminoazobenzene, an azo dye known as butter yellow because of its color, is given by mouth to rats fed on a diet of rice, cancer of the liver regularly develops. If, however, yeast or members of the vitamin B complex are added to the rice diet, no cancer occurs (Sugiura and Rhoads). This is the first instance in which experimental cancer has been prevented by a dietary constituent, deficiency of which acted as a conditioning factor. It would seem that the carcinogenic chemical took the place of the vitamin in the cell, thereby upsetting the regulatory mechanism. Choline deficiency in rats over a prolonged period may result in cancer (Copeland and Salmon). In 40 per cent of such animals carcinoma of the liver developed and in 38 per cent carcinoma of the lung. In those peoples (Bantus, Javanese, Chinese) with a high incidence of cancer of the liver, the diet is very low in vitamins.

**Chronic Irritation.**—In the past there has been no bogey-man of cancer against which more stones have been thrown than that of chronic irritation. The term is so vague that it is not easy to discuss it. There is the occasional instance in which cancer is preceded by and associated with the presence of a chronic irritant. Two examples which deserve mention are gall stones and cancer of the gall bladder on the one hand and the ova of bilharzia and cancer of the urinary bladder on the other. It is inconceivable that these inert objects could "irritate" the epithelium so as to make it neoplastic. An irritant causes inflammation, not cancer, but prolonged destruction of tissue demands constant replacement of parts, and it is possible that when this is continued over an extended period the regulating mechanism may become upset with resulting neoplasia. Such constant destruction and repair with consequent unstable cellular equilibrium may occur in ulcers of the mouth, the tongue and the stomach.

**Heredity.**—In the experimental animal heredity can be made to play an important part by selective breeding. Maude Slye and many others have shown that inbreeding can bring out not merely general susceptibility to cancer but also organ susceptibility. It has been truly said that pure strains of animals of known hereditary tendencies are as important for cancer research as pure chemicals are for the chemist. A race of mice can be bred all of which will die of cancer of the breast. But consideration of Bittner's milk factor makes one wonder to what degree the examples of hereditary cancer in animals are due to true gene mutations or whether they can be explained by some extrachromosomal transmissible factor.

When we come to heredity in human cancer it is usually difficult and often impossible to be sure of the facts, as we are not dealing with pure genetic strains. There are, however, reports of "cancer families" which must be accepted in which cancer appears in every generation, and in some families every member will die of the disease if he lives long enough. Two of the best examples of tumors showing a hereditary tendency are neuroblastoma of the retina and malignant papillomata of the large bowel. From the practical standpoint it may be said that the occurrence of an

occasional tumor or tumors of different types in a family is of little significance, but that the frequent occurrence of one type of tumor points to a strong cancer disposition.

The *age incidence* of cancer is striking, for it occurs at the two ends of life. At least 50 per cent of the cases occur after the age of sixty, although this age group forms only a small fraction of the total population. The reason for this is not clear. In families with a marked cancer disposition the age of onset is much earlier, as in the family described by Lescheziner where a mother and three daughters died of cancer of the breast at the ages of twenty-two, twenty-one, nineteen and fourteen years respectively. At the other end of life there is a small group of tumors which appear to be congenital, being present at birth or developing in early childhood. Examples are retinoblastoma, neuroblastoma of the adrenal medulla and Wilms' tumor of the kidney. Other malignant conditions such as glioma of the brain, sarcoma of the bone and leukemia may develop either in childhood or adult life.

*Multiple tumors* in different organs are not common. It almost appears as if the development of cancer in one organ conferred a certain immunity on the body so that another cancer does not develop. When a cancer has been cured this is no longer true, and a new tumor may develop in another organ. In this connection it may be noted that the incidence of cancer in the two sexes is about the same, in spite of the fact that cancer of the breast and uterus are so common in women. The total incidence of cancer is about the same in different countries although the incidence in different organs may vary widely. An animal which has developed a tar cancer cannot develop another as the result of a second tarring, nor can tar cancer be induced in an animal with spontaneous cancer. All of these facts suggest that some form of immunity may be developed in response to the development of a tumor, which some day might form the basis of a test for cancer.

The question of *spontaneous cure* may be considered in connection with immunity. Most of the reports in the medical literature should be regarded with grave suspicion. Unless biopsy has confirmed the diagnosis of cancer the case is worthless. Occasionally, however, the evidence is so well attested that to reject it flatly as impossible appears to be unscientific. I have seen more than one such case in my own experience. In these rare cases the fire seems to burn itself out.

**Transplantation of Tumors.**—All of the earlier experimental work on cancer was done on transplanted tumors. In the past it was only possible to transplant a tumor to another member of the same species, and because of this strict specificity it was not possible to work with human material. This obstacle has been overcome in three very different ways. (1) Greene, by employing the anterior chamber of the animal's eye, succeeded in transferring human cancer to rabbits and guinea-pigs. The host animal merely acts as a culture medium for the tumor cells of the original animal. (2) Tissue resistance can be overcome by preliminary radiation of the animal with destruction of the lymphoid tissue which seems to play some part in the immunity mechanism. The same is true if very young animals, generally weanlings, are employed. (3) Green and Whiteley, followed later by Hoch-Ligeti and Hsü, Toolan and others, found that the administration of

cortisone broke down the strict specificity, so that transfer of cancer could be made from rat to mouse and from man to mouse. As the result of this preliminary treatment there was none of the cellular reaction around the transplant which is often so marked in the controls. The cortisone appears to depress antibody production to heterologous antigens in the transplanted tumor. This may be due to the great reduction in the number of lymphocytes which are known to produce antibodies, and this reduction in turn may be caused by inhibition of mitoses in the short-lived lymphoid cells. The ability to grow human cancer in the laboratory animal should prove of great value in the experimental investigation of the restraint of growth by chemotherapeutic and other methods.

**Cancer Therapy.**—At the present time cancer can be treated effectively by surgical removal or by radiotherapy (*X*-rays or radium) or both. But this is only possible if the tumor is still localized when the patient is first seen by the doctor. Moreover it is impossible to avoid the destruction of normal tissue both by the surgeon's knife and by the even more lethal weapon of radiation. The ideal therapeutic agent would be one with a selective action on and affinity for malignant cells while leaving normal cells untouched. This may seem to be a vain hope, but the same could have been said of the chemotherapy of bacteria in the tissues before the introduction of the sulfonamides and the antibiotics.

Carcinogenic substances which upset the delicate chromosomal nucleoprotein mechanism may also be made to be carcinolethal. The best known example is radiations which may both cause and cure cancer, but it is also true of chemical agents and of viruses, which are radiomimetic in that they have this double action. What is potent for evil may also be made powerful for good. The carcinogenic hydrocarbons and certain vesicants such as mustard gas and nitrogen mustard may inhibit both normal and malignant growth. We have already seen that an abnormal precursor of nucleic acid, 2:6-diaminopurine, can cause selective injury to cancer cells both in tissue culture and in transplanted tumors in the experimental animal. Many other analogues of adenine have been prepared, and it is not too much to hope that future progress in the chemotherapy of malignant disease may follow the same fruitful line as has been seen in the chemotherapy of bacterial infection.

Viruses may be carcinogenic or carcinolethal. Some viruses enter cancer cells and destroy them. Unfortunately all the cancerotropic viruses are also neurotropic; they attack the cells of the central nervous system as well as those of the tumor, so that they kill the mouse as well as the cancer. But continued growth of a virus on a tissue by repeated passage will increase its tropism or affinity for that tissue. In this way a virus can be trained to adapt itself to cancer cells and to lose its affinity for nerve cells, just as a dog might be trained to prefer fish to meat. The virus of Russian encephalitis, on which much of the work has been done, can be trained by continued culture to cure leukosis of fowls, a form of cancer, in 100 per cent of cases without injury to the fowl. Higgins and Pack report a case of malignant melanoma in which five and one-half years intervened between the first and second group of skin metastases. No such interval was observed in 1000 other cases of this disease. Enquiry revealed the fact that

the patient had received rabies vaccine after being bitten by a dog. Of thirty patients with melanoma treated with the vaccine eight showed marked regression of the metastases.

## THE PATHOLOGICAL DIAGNOSIS OF CANCER

The recognition, especially the microscopic recognition, of malignancy may be very easy, but it may be exceedingly difficult, and the best pathologists will be found to differ in their diagnosis of individual specimens. Two pitfalls may be mentioned at this point; these are carcinoma in situ and benign epithelial invasion.

*Carcinoma in situ* is a term suggested by Broders for a condition in which the epithelium shows definite evidence of malignancy such as irregularity in size and shape of the cells, hyperchromatism, etc., but definite invasion of the surrounding tissue has not occurred. (Fig. 130). My former associate, Dr. William Anderson, has suggested the graphic metaphor of a number of wild horses running around in a corral looking for a way to get out. Whether or not they will inevitably escape, or whether the cells may calm down and the condition be reversible, is an important matter on which opinions differ. A *precancerous state* is one in which there are transitional stages between the original normal histological picture and a definite picture of carcinoma in situ. It is evident that here also there is plenty of room for difference of opinion. The term precancerous is also applied, more particularly by the clinician, to a condition in which a benign lesion subsequently develops into a malignant one with a high degree of frequency. Examples are nevus of the foot and multiple papillomata of the bowel. *Benign epithelial invasion* is the converse of carcinoma in situ. Here the epithelium retains its normal character, but has penetrated deeply into the underlying tissue. The best example is seen in the gall-bladder, where newly-formed glands may penetrate as far as the serous coat without the condition becoming malignant (Fig. 131). Other examples are seen at the edge of a chronic ulcer of the skin or the stomach, and in the uterus, ureter and other organs lined by epithelium.

**Biopsy Examination.**—A biopsy is the examination of a piece of tissue removed during life. The fate of the patient may depend on a correct report, because the treatment will be determined by the presence or absence of malignancy. In superficial lesions where only a portion may be removed the section must go deep. A shaving of the surface is worse than useless. A frozen section is usually made, so that an immediate report can be given to the surgeon, to be confirmed later by the more reliable paraffin technique. It is in lumps of the breast that the biopsy has its greatest use.

Tumors of lymph nodes are particularly hard to diagnose by physical examination, so that the clinician frequently turns to the pathologist for assistance. But removal of a lymph node in diseases of the lymphatic system is much overdone. If the physician is in doubt, the pathologist is also likely to be in difficulty. Examination of the white cells of the blood for leukemia should never be omitted before subjecting the patient to the discomfort and expense of a biopsy. On no account should an inguinal

lymph node be taken, because it so often shows the changes of previous inflammation which confuses the microscopic picture.

**Cytological Diagnosis.**—The pathologist reports cancer in a tissue partly from a study of the cells, but mainly from a consideration of an upset in the normal histology of the part, more particularly invasion of the deeper tissues by tumor cells. He can also offer an opinion on detached or exfoliated cells. This is the study of *exfoliative cytology*, which depends on the fact that cancer cells lose the adhesiveness or stickiness characteristic of normal cells, and therefore tend to be cast off or exfoliated from a surface. The cells are contained in exudates, secretions, washings, or scrapings.



FIG. 130.—Carcinoma in situ.  $\times 125$ .



FIG. 131.—Benign epithelial invasion in gallbladder. New glands have penetrated to serosa  $\times 12$ .

The material may be examined in smears by the method which Papanicolaou introduced for the study of vaginal secretion, or it may be coagulated by picric acid and treated as a block of tissue as suggested by Hunter and Richardson. Most pathologists find the latter or cell block method more convenient and reliable. By this technic it is possible to make a correct diagnosis in a very high percentage of cases in cancer of the cervix and bronchus; it is of value also in the investigation of suspected early cancer of the stomach, bladder, kidney and prostate, and in the study of pleural and peritoneal effusions. The errors are false negatives and false positives which cannot well be discussed here.

**THE RELATIVE FREQUENCY OF TUMORS.** Here a few words may be devoted to the relative frequency as regards site of malignant tumors. The writer has found it impossible to obtain reliable data as to the frequency of all malignant growths. The figures of the radiotherapist, the surgeon, the internist, the gynecologist, and the pathologist in the autopsy room naturally differ profoundly. Thus cancer of the skin, one of the commonest forms of malignant disease, is seldom seen on the post-mortem table. The following facts relating to the distribution of cancer deaths in Canada are taken from the publications of the Dominion Bureau of Statistics for the period 1931-1944. In both men and women cancer of the digestive tract is the most common, accounting for 52 per cent of the deaths. Among women the next most frequent sites are the breast (18.8 per cent) and uterus (15.6 per cent). Among men cancer of the genitourinary system including the prostate is second in order of importance (16.2 per cent). Cancer of the prostate alone accounted for 8.9 per cent of male deaths. Other approximate figures are stomach 23, lung 6, rectum 4.5, mouth 4, pancreas 3, esophagus 2, brain 2, skin 2. It is important to realize that statistics of this type, based on information in death certificates, contain many fallacies. The records of any autopsy department, for instance, would show a much higher percentage of cancer of the lung, which in my experience heads the list of fatal cancers in individual organs. Regarding total incidence it may be said that in a population of 1,000,000 persons approximately 2,300 new cases of cancer (excluding the lymphomas) will appear annually.

**PROGNOSIS IN CANCER.** It is obviously impossible in such a work as this to enter into a detailed discussion of the prognosis of cancer. For one thing methods of treatment, both by surgery and radiation, are so continually improving that what may be said today is out of date tomorrow. The important thing for the student to realize is that the prognosis in malignant disease no longer presents the dark picture it used to. Over-all figures are of little value, because the outlook varies so enormously in different forms of cancer. Cancer of the skin is a readily curable disease, whereas in some other forms the prognosis is very bad.

The figures of a cancer clinic in Ontario between the years 1936 and 1945 (McCormick) may be of interest. In this clinic 38 per cent of all patients seen with cancer were alive and seemingly well five or more years later. Of the patients treated for cure rather than merely for palliation (58 per cent) there was a 69.4 per cent five-year survival.

**IS CANCER INCREASING?** This question, so often asked, is not easy to answer without giving a false impression. Undoubtedly there are many more deaths from cancer than there used to be. In Canada in 1901 the cancer death rate was 46.8 per 100,000; in 1921 it had risen to 75 per 100,000, an increase of 62 per cent. But in deciding whether the increase is real or apparent, such factors as the general age of the population have to be borne in mind. The larger the proportion of old people, the higher will the cancer rate be. The truth appears to be that cancer is increasing both actually and relatively because of the great saving of life in the early years. It may also be said that the cancer rate is an index of the public health organization of a country; cancer is the legacy of preventive medicine. In the Vision of Mirza Addison describes the masses of mankind crossing the bridge of life which spans the river of death and falling into the dark flood below. In the bridge there are many trapdoors—infantile mortality, typhoid, malaria, smallpox—through which the unwary traveler may drop, but these seldom open now. So large numbers approach the end of the bridge and drop through a small number of wide doors, such as apoplexy, coronary occlusion and, above all, cancer.

## THE EFFECT OF RADIATION ON TUMORS

No aspect of the study of tumors is of more practical importance than the effect of irradiation, whether by roentgen-rays or the gamma rays of

radium. Only the general principles can be indicated here, but each kind of tumor and indeed tumors of each individual organ have to be studied separately. The chief methods used are: (1) external radiation (roentgen-rays and radium), (2) surface application (radium), and (3) interstitial radiation (radium). For widespread malignant processes such as lymphosarcoma and leukemia roentgen-rays provide the more practical method. The use of properly screened gamma rays avoids necrosis, but permits the specific selective action of the rays on the tumor cells. As Colwell remarks: "The aim of all modern radiotherapy is to eliminate this indiscriminate caustic action, and by adequate filtration and graduated exposure to administer such doses as shall have the maximum destructive effect upon the neoplastic cells with the minimum of danger to normal tissues." The effects of radiation depend partly on the action on the tumor cells, partly on the action on the tissues.

1. EFFECT ON THE TUMOR CELLS.—The effect may be studied in tissue culture or in the body. This effect is twofold: (1) arrest of cell activity, and (2) degeneration and destruction of cells. Actively growing and dividing cells are much more sensitive than ordinary cells. This is expressed in the "Law of Bergonié and Tribondeau," that the radio-sensitiveness of any tissue depends on its reproductive activity. The more numerous are the mitoses, the more sensitive is the tissue. It follows that granulation tissue, embryonic tissue, and undifferentiated rapidly dividing cancers are most radio-sensitive. Partial or complete degeneration of the cell occurs. The nucleus breaks up and undergoes chromatolysis, the cytoplasm becomes granular and vacuolated, the cell dies and disappears. It has already been suggested (page 233) that radiation interferes with the metabolism of the nucleoproteins of the nuclear chromatin, upon the activity of which cell division is dependent. The name of Strangeways of Cambridge must always be associated with the work on tissue culture of tumors, and Canti has made moving pictures of the cellular response to radiation which for drama and thrill equal any product of Hollywood. Many of the cells die a sudden death, and can be seen on the screen actually to "explode." The degree of sensitiveness depends on the position of the cell in the mitotic cycle, the most sensitive period being just before the commencement of mitosis. All the cells in the culture are never killed, even though the dose largely exceeds the therapeutic limit, but the lethal effect is much greater than would at first sight appear. When subcultures are made of the irradiated culture it is found that the remaining cells have lost their power of reproduction, although this loss may not become apparent until the culture has passed through a dozen generations. As a result of this delayed effect all the cells ultimately die.

Shields Warren and his associates have introduced a new technic for the preparation of sections, which consists of freezing and drying the tissue followed by dry cutting and mounting. As chemical fixatives and aqueous solutions are not used, there is no diffusion of water-soluble compounds. By this method there is a more delicate preservation of nuclear details such as is seen in living cells under the phase-contrast microscope. When tumors of rats and mice are examined five minutes after contact with radioactive isotopes and three hours after external radiation, cytologic



changes are seen which are not demonstrable by the usual method of preparation. These changes serve to distinguish the radio-sensitive from the radio-resistant cells. In the radio-sensitive cells there is a striking production of large intranuclear vacuoles which may rupture the nuclear membrane. Most of the nuclear membranes are irregular and wrinkled. The radio-resistant cells show a very slight degree of similar changes, so that the difference is quantitative rather than qualitative. The Feulgen reaction shows the desoxyribonucleic acid in the nucleus to be decreased in proportion to the degree of vacuolization. Radiomimetic chemicals such as aminopterin which are lethal to tumor cells fail to produce vacuolization, but colchicine causes the same changes as radiation and is, therefore, truly mimetic.

Two types of effect may be obtained, depending on the method used. (1) *Autolytic degeneration* and softening. This is best seen in anaplastic undifferentiated tumors such as lymphosarcoma and Ewing's tumor of bone, but by using appropriate screening a similar effect may be produced in cancer of the mouth, tongue, tonsil, and cervix uteri. (2) *Growth restraint*. Resistant tumors such as osteogenic sarcoma of bone when radiated over a long period may cease to grow, though failing to disappear. They have become quiescent, their malignancy is greatly diminished, and they can then be removed surgically with greater safety.

2. **EFFECT ON THE TISSUES.**—Radiation acts as an irritant and produces an inflammatory reaction in the stroma of the tumor and in the surrounding tissue. An exudate is formed consisting of serum and cells. The cells are at first polymorphonuclear leucocytes, but these are replaced by lymphocytes, plasma cells, and eosinophils. These cells appear to play some part in a defense reaction. The fibroblasts are stimulated to proliferate and lay down collagen fibrils, so that a dense fibrosis is the result. Perhaps the most important reaction is in the vessels. Both the bloodvessels and lymphatics show a marked obliterative endarteritis, with the result that the lumen is either greatly narrowed or completely occluded. Thrombosis is common. The result of these vascular changes is twofold. (1) The lack of blood supply leads to degeneration in the tumor, and some of the cellular changes are due to ischemia rather than to the direct action of the rays. (2) The lymphatics and blood channels being closed, embolism is not liable to occur, so that the surgeon may safely postpone operating while irradiation is being carried out, and when the tumor is removed there is less chance of embolic spread of cancer cells.

The part played by the tissue reaction explains some of the difficulties encountered in treatment. A cancer may be radio-sensitive, but when it invades bone it becomes radio-resistant. Rodent ulcer is a good example of this. The interstitial reaction is not able to take place in the non-vascular dense bone. Cancer of the breast responds rather poorly to radiation, because the breast is so rich in fat, and this tissue with its limited blood supply seldom shows a marked reaction.

**Radio-Sensitivity.**—Tumors vary in their sensitivity to radiation. The variation is mainly an intrinsic factor, with characteristic radio-sensitivity as a property of each type of tumor cell. As Ralston Paterson remarks, intrinsic sensitivity is a characteristic of each "species"—squamous cell

carcinoma, basal cell carcinoma, adenocarcinoma, lymphosarcoma, melanoma, etc. The sensitivity remains relatively constant within each species, not varying with such histological features as differentiation, anaplasia, number of mitoses, etc. The purpose of the histological grading of tumors is an indication of the degree of malignancy, not an index of radio-sensitivity. Thus a highly differentiated squamous cell carcinoma will respond as completely as a highly anaplastic one. It is true that the more differentiated the cells and adult the type of tissue, the more radio-resistant is the tumor, and vice versa, but the rate of regression is not a reliable indication of the actual sensitivity of the tumor *as a whole*.

Malignant tumors may be divided according to their radiosensitivity into three main groups: (1) highly radiosensitive: lymphosarcoma, multiple myeloma, lymphoepithelioma (transitional-cell carcinoma), embryonal carcinoma; (2) moderately radiosensitive: epidermoid carcinoma, and the less differentiated forms of adenocarcinoma; highly radioresistant: fibrosarcoma, osteosarcoma, neurosarcoma, melanoma, glioma, adenocarcinoma (except adenocarcinoma of the thyroid).

As Glucksmann points out, radiosensitivity as measured by the rate of macroscopic shrinkage bears no close relationship to radiocurability, with the single exception of basal-cell carcinoma of the skin. "Radio-sensitive tumors are the 'miracles' of radiation, the source of conceit in the inexperienced radiotherapist, and the greatest source of disappointment when apparently brilliant successes become in due course dismal failures" (Sir Stanford Cade). Radiosensitivity depends largely on the preponderance of short-lived undifferentiated cells and is therefore linked with anaplasia. Radiocurability is related rather to differentiation. Even in normal tissues such as the cervix uteri radiation may change the extent and type of differentiation. In malignant tumors the promotion of differentiation and with it the sterilization of the tumor cells is of great importance.

**Classification.**—Much has been written regarding the classification of tumors and many classifications have been suggested. The most useful working method is to try to determine the tissue, the type cell, from which the tumor arises. This way may be easy or it may be difficult or impossible. The more undifferentiated and anaplastic the tumor, the more difficult is it to recognize the type cell. In the description of the various forms of tumors some will only be referred to; these are more conveniently considered in connection with the organs from which they grow.

The classification to be used is as follows:

- |                             |               |
|-----------------------------|---------------|
| 1. Connective-tissue tumors |               |
|                             | { Fibroma     |
|                             | { Lipoma      |
| A. Innocent                 | { Myxoma      |
|                             | { Chondroma   |
|                             | { Osteoma     |
| B. Malignant                | { Sarcoma     |
|                             | { Chordoma    |
| 2. Muscle-tissue tumors     | { Leiomyoma   |
|                             | { Rhabdomyoma |

3. Angioma { Hemangioma  
Lymphangioma
4. Tumors of hemopoietic tissues
  - A. Benign lymphoma
  - B. Malignant lymphoma { Lymphosarcoma  
Hodgkin's disease  
Leukemia  
Multiple myeloma
5. Pigmented tumors { Nevus  
Melanoma
6. Nervous-tissue tumors { Glioma  
Neuroblastoma  
Retinoblastoma  
Ganglioneuroma
7. Epithelial tumors
  - A. Innocent { Papilloma  
Adenoma
  - B. Malignant Carcinoma
8. Special forms of epithelial tumors { Hypernephroma  
Choriocarcinoma  
Adamantinoma
9. Teratomas

## CONNECTIVE-TISSUE TUMORS

### INNOCENT CONNECTIVE-TISSUE TUMORS

**Fibroma.**—The type cell of the fibroma is the fibroblast. It is composed of fibrous tissue. The proportion of cells to collagen fibers varies greatly. *Hard* fibromas are acellular with abundant collagen. *Soft* fibromas are highly cellular. Of course, there are all grades. The more highly cellular the tumor, the nearer does it approach to malignancy. It might be thought that the fibroma would be a common tumor. On the contrary, it is quite rare in a pure form.

*Gross Appearance.*—The gross appearance is that of an encapsulated rounded tumor, firm, white in color, the cut surface being flat and intersected with glistening bands. *Microscopically* it presents intersecting bundles of fibers between which are a varying number of fusiform cells. (Fig. 132.)

*SITES.*—In the *skin* there may be hard or soft fibromas. As the latter arise from cutaneous nerves they will be considered in connection with neurofibromas. Fibromas of *mucous membranes* are found in the submucous coat of the stomach and intestines. They often project into the lumen and become pedunculated. *Visceral* fibromas occur in the ovary, kidney, and other organs, usually remaining quite small. Fibromas growing from the nasopharynx may attain a large size and threaten the life of the patient.

Fibroma of the *abdominal wall* is called a desmoid tumor (*desmos*, band or fiber). It grows from the sheath of the rectus abdominis, and may attain a considerable size and invade the muscle. The muscle fibers enclosed in

the tumor undergo a peculiar change with the formation of multinucleated masses like foreign body giant cells. About 80 per cent of the cases occur in women who have borne children. In the remaining cases there is usually a history of trauma to the abdominal wall.

Fibroma of *nerve* may be divided into cutaneous neurofibroma and neurofibroma of the subcutaneous and deeper nerve trunks. (1) The *cutaneous neurofibroma* may be single, forming a firm and often very tender nodule in the skin. The tumor arises from the connective-tissue sheath of the nerve.

*Multiple neurofibromata* constitute the condition known as von Recklinghausen's disease, or molluscum fibrosum. There may be hundreds of tumors. They usually grow from cutaneous nerves and form soft nodules in the skin, but they may grow from the deep nerves and cranial nerves. The skin is often pigmented in patches. Death is not uncommonly due to sarcomatous change in one of the tumors.

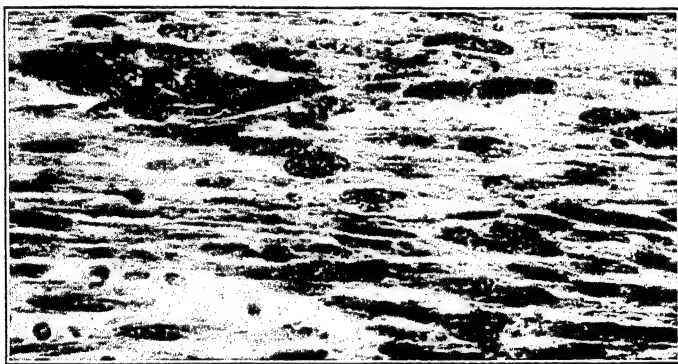


FIG. 132.—Fibroma showing fibroblasts and fibers.  $\times 400$ .

(2) *Neurofibroma of the deeper nerves* grows from the subcutaneous nerves and the deeper trunks. It is much less common than the cutaneous form, but is of importance in that it has a strong tendency to become malignant. The condition is described more fully under the heading of Neurosarcoma or Neurogenic Sarcoma. A *plexiform neuroma* is a diffuse over-growth of the endoneurium of the nerves in the subcutaneous tissue. It is made up of coiled and thickened nerve trunks, many of which can be dissected out. The usual site is the head and neck.

*Xanthoma*.—As its name indicates, a xanthoma is a yellow tumor (*xanthos*, yellow), and has the general structure of a fibroma. At least three distinct forms can be distinguished.

1. *Xanthelasma*, by far the commonest variety, is not a real tumor but a degeneration of the muscle of the eyelid. It occurs as small yellow nodules on the eyelid in elderly persons.

2. *Xanthoma multiplex*, also known as X. diabetorum, in which groups of yellow nodules are scattered over the surface of the body. It is associated with a

high blood cholesterol (the yellow color is due to cholesterol), and is therefore found in diabetes and obstructive jaundice.

3. *Large xanthomas* are rare tumors which occur in connection with tendon sheaths, and which may resemble giant-cell tumors.

All of the tumors are of a bright yellow color. They consist of connective-tissue cells greatly distended with lipid droplets (cholesterol ester) so that the cell has a pale and foamy appearance. In addition to these "xanthoma cells" there are fibroblasts and foreign body giant cells. The latter are especially numerous in the single large tumors, and these tumors often contain much blood pigment. In some cases a striking feature is the so-called Touton giant cells, which are characterized by a remarkable ring of nuclei right around the periphery of the cell. They may be very numerous. I have not met with them in any other condition.

In some forms of xanthoma the basis of the condition may be a general disturbance of lipid metabolism associated with hypercholesterolemia. In others the defect may be intracellular, involving certain cells of the reticuloendothelial system.

**Lipoma.** A lipoma is a tumor composed of fat. It is a common tumor, occurring mainly in the subcutaneous tissue of the neck, shoulders, back, and buttocks. Occasionally it grows from the mesenteric and retroperitoneal fat, and still more rarely from the submucous coat of the stomach and intestine where it may form a polypoid mass. The "diffuse lipoma" of the neck is not a neoplasm but a lipomatosis. A lipoma does not waste when the rest of the fat wastes in cachectic diseases.

A lipoma is a soft circumscribed, lobulated, encapsulated tumor, easily shelled out. It is not attached to the deep fascia, but the overlying skin is often dimpled, owing to fibrous bands passing between it and the tumor. The lipoma is a very innocent tumor, but retroperitoneal and perirenal lipomas may rarely contain embryonic portions which grow rapidly and infiltrate. These tumors are called liposarcomas.

**MYXOMA.** A myxoma is a connective-tissue tumor with the structure of umbilical cord. It very rarely occurs as a pure tumor, but mucoid or myxomatous degeneration is common in connective-tissue tumors, both innocent and malignant. The appearance of myxomatous degeneration in what appears to be an innocent connective-tissue tumor is always suggestive of a malignant change. A definite sarcoma showing myxomatous tissue is called a *myxosarcoma*. The *microscopic* appearance is that of Wharton's jelly in the umbilical cord. Branched connective-tissue cells are scattered through a jelly-like or mucoid matrix. This material can be stained with mucicarmine.

**Chondroma.**—A chondroma is a tumor composed of cartilage. It is hard, bluish-gray in color, and translucent like normal hyaline cartilage. This, and the fact that it is well lobulated and so encapsulated that it is readily shelled out, make recognition easy. Microscopically it differs from normal hyaline cartilage in that the cells are arranged singly instead of in groups. (Fig. 133.) Being non-vascular it is very liable to myxomatous degeneration. It often becomes calcified. It grows from the ends of long bones in young persons, originating from the epiphyseal cartilage. When the bone stops growing, the tumor also ceases to grow and becomes calcified or ossified. These tumors also grow from the bones of the hands and feet, and from flat bones like the sternum and pelvis. The latter may attain a great size, and sarcomatous change is common.

Cartilage is found in developmental tumors (embryomas) of the testicle and in mixed tumors of the salivary glands. These should not be called chondromas. Multiple chondromas (multiple cartilaginous exostoses) will be considered in relation to diseases of bone.

**Osteoma.**—New formations of bone are common (callus of fractures, exostoses, etc.), but true osteomas, like true fibromas, are comparatively rare. The *cancellous osteoma* is made up of cancellous bone. It originates from the epiphyseal cartilage as a chondroma, and though converted into bone a cap of cartilage covers the growing tip. As the bone grows in length the tumor becomes separated from the epiphyseal line. A *subungual exostosis* is a cancellous osteoma which grows from the dorsal surface of the terminal phalanx of the big toe. It forces the nail up and causes much pain. A *compact osteoma*, also called an ivory exostosis because of its hardness, grows from the vault of the skull. It is a sessile tumor which may press on the brain or invade the orbit.

#### MALIGNANT CONNECTIVE-TISSUE TUMORS

**Sarcoma.**—A sarcoma is a malignant tumor of connective tissue. It forms a large heterogeneous group, the limits of which should be greatly narrowed. Many tumors are called sarcoma although they are not connective-tissue tumors nor do they behave like them. Such are lymphosarcomas, melanotic sarcoma, myosarcoma. None of these will be considered here, and where possible the names should be changed. It is not always realized by the student commencing the study of pathology that carcinoma is an infinitely more common malignant tumor than sarcoma.

**MALIGNANCY.**—The malignancy of sarcoma varies enormously. This adds to the difficulties of microscopic diagnosis. The more malignant forms are easily recognized as such, but as we approach the dividing line we encounter a picture which on the one hand may resemble a cellular fibroma and on the other hand granulation tissue. Only long experience will give the pathologist the feeling that a lesion is malignant, a feeling which he may find difficult to justify in words. With repeated removal of a recurring tumor the histological picture may alter markedly for the worse.

**Gross Appearance.**—The sarcomas vary so greatly that no general description can cover the group, but they have certain points in common.



FIG. 133.—Chondroma.  $\times 240$ .

A typical sarcoma has a fleshy appearance (*sark*, flesh). It forms a bulky mass which is more sharply demarcated from the surrounding tissue than is a carcinoma. The more cellular forms may resemble the white matter of the brain. The tumor varies much in consistence, but it is often soft like the brain. The cut surface is homogeneous, and this is one of its chief characteristics. But degenerations are common, and these may interfere with the homogeneous character of the tumor. The growth of the tumor may outstrip its blood supply, with the result that a species of infarction occurs. Necrosis, mucoid or myxomatous softening, and actual liquefaction are frequent. The most common of these changes is hemorrhage from the abundant and very thin-walled blood vessels.

*Microscopic Appearance.* The less differentiated forms are highly cellular and the stroma may be so scanty as to be indistinguishable. The more differentiation, the more abundant and characteristic does the stroma become. Thus in the osteosarcoma there is osteoid tissue or bone between the cells. The general histological arrangement of a sarcoma differs fundamentally from that of a carcinoma in the same way that connective tissue differs from epithelium. The cells of a carcinoma are arranged in groups separated by a stroma, but the stroma does not penetrate between the individual cells of the group. This is called an alveolar arrangement, and resembles that of the epithelium from which the tumor arises. In a sarcoma, on the other hand, there is no alveolar grouping; the cells are uniformly distributed, and are separated by a stroma. This may be very abundant as in bone sarcoma, or it may be so fine that it requires special staining methods to bring it out. Sarcoma cells have other mesoblastic characteristics. They tend to have poorly defined borders compared with carcinoma cells, and extensions of the cytoplasm form an intercellular matrix. Numerous blood vessels, often mere capillaries or sinusoids, penetrate the tumor, whereas in carcinoma the vessels are confined to the regular stroma which separates the groups of cells. Thus necrosis is more apt to occur in carcinoma, as the growth of cells outstrips that of the vessels. Sarcoma grows expansively on this vascular framework, and it is small wonder that hemorrhages are frequent. Carcinoma tends to grow rather by infiltration. Mitotic figures are significant in mesenchymal tumors, but much less so in epithelial tumors; they are often seen in inflamed and irritated epidermis.

The type cell may be the fibroblast, the osteoblast, the cartilage cell, etc. In the most undifferentiated forms the type cell cannot be recognized. Many of these tumors are polymorphic, showing a variety of cells. Mitotic figures are very numerous in the rapidly growing sarcomas, scanty in the slowly growing ones. Their presence is of great value in the differentiation from a cellular fibroma, but it must be remembered that mitotic figures may be present in rapidly growing granulation tissue. Tumor giant cells form a feature of some highly malignant sarcomas. If the tumor becomes infected the giant cells may phagocytose many of the leucocytes, a rare occurrence. (Fig. 134.)

*SPREAD.*—A sarcoma grows *expansively* so as to form a bulky mass, but it also *infiltrates* the surrounding tissue. The rate of growth varies greatly. Unsuccessful (incomplete) operative interference is often followed

by a great increase in the rate of growth. A rapidly growing sarcoma may sometimes outstrip its blood supply, so that the tumor may halt and even retrogress. Infiltration of the surrounding tissue occurs. The tumor cells creep along the fascial plane, between the muscle fibers, through the Haversian canals of bone, etc. Owing to this tendency removal is likely to be incomplete and recurrence is very common.

*Distant spread* takes place by the blood vessels. The vessels are so abundant and so thin-walled, and the sarcoma cells so readily invade them that early blood dissemination is inevitable. Metastases are first formed in the lungs, but the tumor cells may pass through the lungs to any of the viscera. Owing to this early spread the lungs should be roentgen-rayed for metastases even in what appear to be the most operable of sarcomas. Spread by lymph stream is uncommon, but may occur in from 5 to 10 per cent of cases.

The *sites* of a sarcoma are varied, since connective tissue occurs in every part of the body. They are especially common in bone, subcutaneous tissue, fascia, and muscle.

Two methods may be used in the classification of the sarcoma. The first is cytological, the second histological. In the first the tissue is named according to the form of cell which predominates, so that we have a round cell (small and large) sarcoma, a spindle-cell (small and large) sarcoma, a mixed-cell sarcoma, and a giant-cell sarcoma. This method is the refuge of the destitute, and should be avoided to the utmost of one's ability. In the second or histological method the tumor is named according to the type of connective tissue from which it arises, so that we have a fibrosarcoma, osteosarcoma, chondrosarcoma, etc. This is the only satisfactory method, but if differentiation has not gone sufficiently far it may not be possible. The interstitial tissue is often more characteristic than the cells of the tumor. *i. e.*, it may be osseous, cartilaginous, collagenous, etc.

**HISTOLOGICAL TYPES OF SARCOMA.**—1. *Fibrosarcoma.*—This is a spindle-cell sarcoma, the type cell being the fibroblast. (Fig. 135.) It is not really a common tumor, as used to be thought. Many malignant connective-tissue tumors formerly regarded as fibrosarcomas are now known to be neurogenic in origin, arising from peripheral nerves. The cells are fusiform, and may be small or large, the latter being the more malignant type. Both the gross and the microscopic features vary much, depending on the degree



FIG. 134.—Phagocytic tumor giant cell.  $\times 600$ .



of anaplasia. In the anaplastic forms the tumor may be very soft, and the cells may be so slightly fusiform that the non-committal name of round-cell sarcoma is applied. The stroma varies. It may be very scanty, or abundant fibrils may be formed so that it may be difficult to distinguish the tumor from a soft fibroma. The presence of mitotic figures is one of the most valuable points. Its behavior is that of a sarcoma of varying degrees of malignancy.



FIG. 135.—Fibrosarcoma. The cells are large and fusiform.  $\times 1000$ .

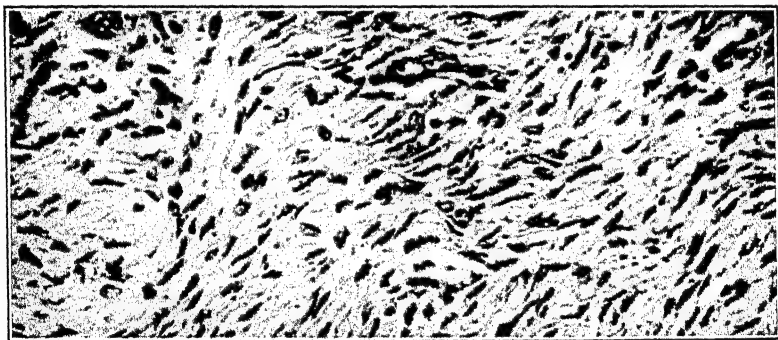


FIG. 136.—Neurogenic sarcoma, showing the fasciculated arrangement.  $\times 300$ .

2. *Neurosarcoma (Neurogenic Sarcoma).*—The term *neurogenic sarcoma* was introduced by Ewing to designate a type of spindle-cell tumor which was supposed to arise from deeply situated peripheral nerves. This concept has become generally accepted to such a degree that the great majority of fibrosarcomas are now regarded as of neurogenic origin. This concept has been vigorously attacked by Stout, who points out that no proof exists of the origin of these tumors from nerve fibers, a view with which the writer is in agreement. The histological feature which is taken as an indication of neurogenic origin is a tendency for the tumor cells to run in interlacing bundles or fasciculi.

At first the neurogenic sarcoma is localized, but with continued growth and especially on recurring it infiltrates the surrounding tissue. The microscopic appearance is in general that of a fibrosarcoma, but the elongated cells are arranged in characteristic intertwining bundles, fasciculi and whorls. (Fig. 136.) The appearance suggests the neurogenic origin, but it may be very difficult to determine the question of malignancy. It is highly radio-resistant, a point of some value in differential diagnosis.

3. *Osteosarcoma (Osteogenic Sarcoma)*.—This is one of the most important and common forms of sarcoma. The type cell is the osteoblast, but it is by the intercellular substance (bone, cartilage) that it is most readily recognized. It is considered together with other bone tumors in Chapter 32.

4. *Chondrosarcoma*.—A chondroma may show evidence of malignancy (rapid growth, irregularity in the size and shape of the cells, mitoses), and is then known as a chondrosarcoma. (Fig. 137.) It arises from a bone,



FIG. 137.—Chondrosarcoma. Great irregularity in size of cells. Compare with Fig. 133 which has same magnification.  $\times 240$ .

often the sternum or pelvis, may attain a huge size, and invades the blood vessels causing pulmonary metastases. The distinction between a chondroma and chondrosarcoma may be very difficult, and the pathologist may have to depend on the clinical course and the gross appearance (invasion, etc.) rather than on the microscopic picture. Myxomatous degeneration should arouse suspicion.

5. *Liposarcoma*.—This tumor is by no means so rare as is commonly supposed; it is easily missed, especially if fat stains are not used. It may occur wherever there is fat, but is commonest in intermuscular tissue, around joints, and in the retroperitoneal and perirenal regions. At first encapsulated, it tends to recur after removal and then becomes infiltrating, so that the prognosis is bad. The microscopic picture varies in different cases, and there may be a most confusing variation in a single tumor. The common cells are spindle cells and large polyhedral cells; the cytoplasm is granular and may or may not contain fat, best shown, of course, by means of fat stains. The pale, swollen, polyhedral cells may resemble epithelial

cells (Fig. 138) and thus suggest secondary renal carcinoma (hypernephroma), a mistake especially likely to occur when the tumor is in bone. Cells resembling fetal fat cells may be present, and tumor giant cells are not uncommon.



FIG. 138.—Liposarcoma. Some cells have granular cytoplasm, others are filled with fat.  $\times 510$ .

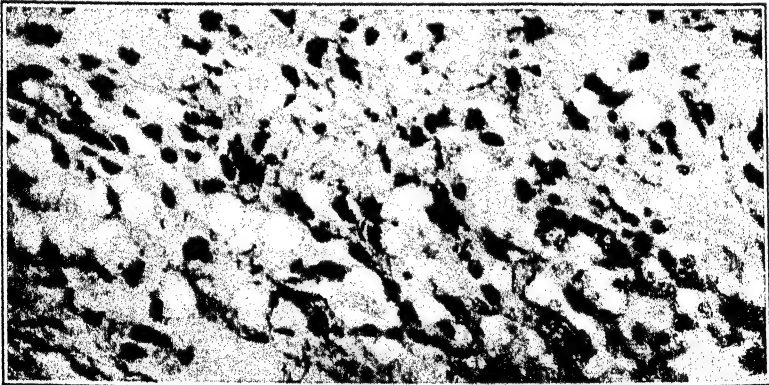


FIG. 139.—Myxosarcoma.  $\times 350$ .

6. *Myxosarcoma*.—This is not a real group, but merely a mucoid or myxomatous degeneration of a sarcoma. (Fig. 139.) The term is useful if it serves to suggest the ominous character of myxomatous change in a connective-tissue tumor.

**CHORDOMA.**—This tumor arises from remnants of the notochord, a structure of hypoblastic origin. It occurs at the upper and lower ends of the vertebral column, because the notochord is enclosed in the bodies of the permanent vertebræ. At the upper end it grows between the pituitary fossa and the foramen magnum, while at the lower end it occurs in the sacro-coccygeal region. It is a very rare tumor of rather low malignancy which spreads by infiltration, and only in the end stages does it form metastases. The tumor, which may reach a large size, is elastic in consistence, and shows numerous areas of translucent chordal tissue separated by patches of hemorrhage. *Microscopically* it consists of large clear cells closely packed together without any intercellular substance. The cells are distended with mucinous material, so that the tumor may be mistaken for a mucoid carcinoma. The cytoplasm, however, has a vacuolated appearance which is very characteristic. (Fig. 140.)

### MUSCLE-TISSUE TUMORS

Just as there are two types of muscle, plain and striated, so there are two forms of myoma or tumors arising from muscle cells. These are the leiomyoma and the rhabdomyoma. To these a third form, the myoblastoma, must be added.

**Leiomyoma.**—The leiomyoma (*leios*, smooth) is an innocent tumor of plain muscle. It is extremely common in the uterus, so much so as to constitute the commonest tumor in the body. The special characters of myomata of the uterus will be considered in connection with diseases of that organ. Leiomyomata are curiously rare in other parts of the body which contain plain muscle. They may occur in the ovary, tubes, and broad ligament, in the alimentary canal where they often form polypoid masses which project into the lumen, and in the bladder and ureters. The muscular walls of the blood vessels are immune.

The *gross appearance* resembles that of a fibroma. The tumor may be of any size, from the very small to the very large. It is hard or at least firm, well encapsulated and easily removed. The cut surface presents a characteristically whorled appearance, due to interlacing bundles of fibers cut in various planes. Degenerative changes are common, such as hyaline and mucoid degeneration, softening, and sometimes complete calcification so that the tumor is converted into a mass of stone.

*Microscopically* the leiomyoma consists of interlacing bundles of plain muscle fibers, separated by a varying amount of fibrous tissue. The cells may be distinguished from those of a spindle-cell sarcoma by the long rod-like nuclei and the absence of mitoses. (Fig. 141.)



FIG. 140.—Chordoma. The clear vacuolated appearance of the cells is characteristic.

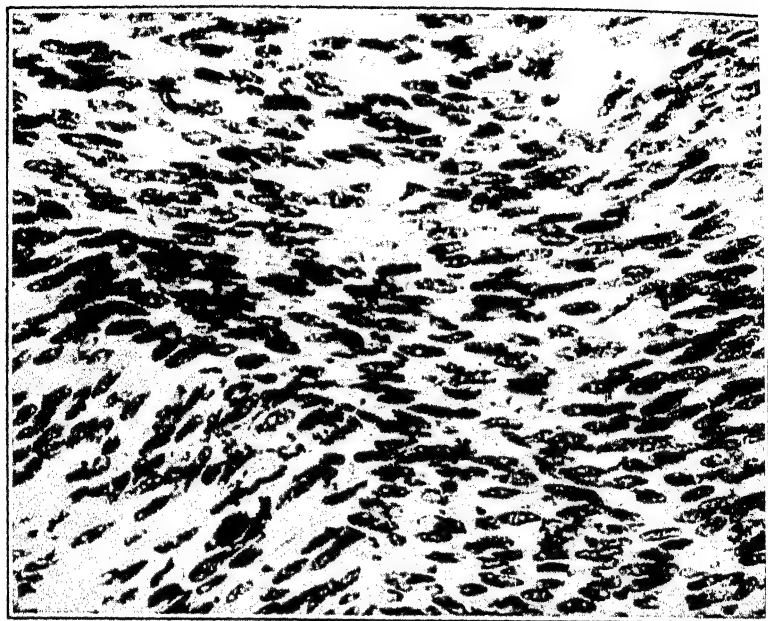


FIG. 141. —Leiomyoma showing plain muscle cells.  $\times 300$ .



FIG. 142.—Rhabdomyoma.  $\times 940$ .

FIG. 143.—Myoblastoma.  $\times 625$ .

Occasionally a part of the tumor may become malignant, and is then called a *malignant myoma* or *leiomyosarcoma*. The nuclei are larger, the cells more active-looking, and mitotic figures can be seen. These tumors seldom give rise to metastases, and may not recur after removal, so that they are usually not highly malignant.

**RHABDOMYOMA.**—The rhabdomyoma is a tumor of striated muscle (*rhabdos*, a stripe). It is curiously rare, indeed extremely so. Nor is it found where it might be expected, *i. e.*, in voluntary muscle. A pure rhabdomyoma is the rarest of all, being practically confined to the heart. Striated muscle is found in embryonal tumors of the kidney, of the vagina of children, and of the testicle. In these tumors the muscle is mingled with other tissues. Only some of the cells are cross-striated. These mixed tumors are highly malignant and metastasize by the blood stream. (Fig. 142.)

**MYOBLASTOMA.**—This tumor of striated muscle was first described in 1926, but 50 cases were reported in the next eight years. The common sites are the tongue, larynx and skin, but it has also been found in the lip, upper part of esophagus, and leg. It consists of polygonal cells with characteristic highly granular cytoplasm. In addition there may be ribbon-like syncytial masses with granular cytoplasm. No cross-striations are seen. It is open to doubt if these tumors really arise from primitive myoblasts, as is generally believed, for they may occur in sites devoid of striated muscle. Moreover they are essentially benign, whereas true differentiated rhabdomyoblastomas are highly malignant. Fust and Custer present evidence suggesting that these tumors are derived from nerves and not from skeletal muscle. The lesions contain concentric masses of granular tumor cells arranged around bundles of axis cylinders with what appear to be frayed nerve sheaths at the periphery. (Fig. 143.)

## ANGIOMA

An angioma is a tumor composed either of blood vessels or lymphatics. The former is called a hemangioma, the latter a lymphangioma. The hemangioma is much the more common, and is commonly referred to as an angioma, the term lymphangioma being reserved for the lymphatic type.

**Hemangioma.**—A hemangioma is a new formation of blood vessels. It may be difficult to distinguish this from telangiectasis, which is merely a dilatation of previously existing vessels. Two types are encountered, the capillary and the cavernous. The former is much the commoner.

**CAPILLARY ANGIOMA.**—This consists of a network of new-formed capillaries filled with blood. (Fig. 144.) The neoplasm affects only one segment of a vessel, from which buds of endothelium grow out and form new vessels. There is therefore a more or less closed system of vessels, not a dilatation of all the vessels of the part. The capillaries appear to arise from a rudiment destined to form blood vessels, and thus form a mass which is to some extent withdrawn from the general circulation, so that any hemorrhage which may occur from it is not necessarily severe. Such a system may be obliterated by making use of the well-known action of radiation on vascular endothelium by which an obliterating endarteritis is produced. The endothelial cells are large and swollen and may be several layers in depth. (Plate VI.) Endothelial proliferation may be so marked that the lumen of the vessels is occluded, and solid masses of cells are formed. Such a con-

dition is often called a *hemangio-endothelioma* or simply an *endothelioma*, for the tumor may appear to be solid and show little evidence of vascular lumen. The new-formed cells may have a whorled arrangement.

The common *site* is the skin, where the angioma forms a bright red, sharply-defined patch level with the surface. It is a congenital condition, usually present at birth, and it may extend so as to cover a large surface. The skin of the face and head is the usual site, but it may occur on any part of the body. On the face it often follows the distribution of the fifth cranial nerve and remains strictly unilateral. These skin angiomas are known as port-wine stains, birth-marks, etc. Capillary angiomas also occur in the mucous membranes of the nose, lip, tongue, gum and rectum, in all of which sites they may be a cause of troublesome hemorrhage. They form soft purplish-red patches which are easily recognized. In the tongue they are a common cause of macroglossia. Multiple angiomata may occur

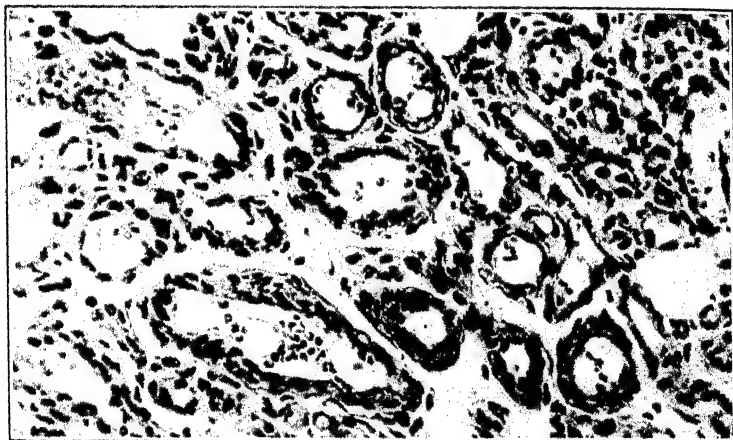
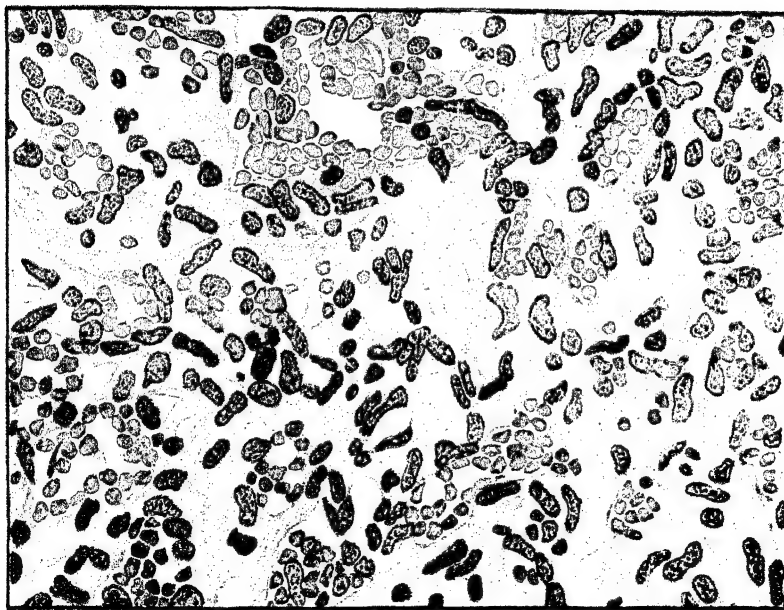


FIG. 144.—Capillary angioma. In addition to many new vessels there is a solid mass of endothelial cells in the upper right hand corner.  $\times 225$ .

in the skin and the mucous membrane of the bowel, giving rise sometimes to intestinal hemorrhage. Angioma of bone is an uncommon but confusing condition, for it may present sheets of lipoid-filled cells resembling those of a hypernephroma. As the lesion causes marked absorption of bone when seen in a roentgen-ray film, it is easy to make the mistaken diagnosis of secondary hypernephroma. Angioma of the brain constitutes one variety of cerebral tumor.

Certain hemangiomas exhibit regressive changes marked principally by fibrosis (Gross and Wolbach). In these *sclerosing hemangiomas* the capillaries become obliterated, whilst segregated groups of endothelial cells remain. In the majority of these cases there are accumulations of lipoid material and hemosiderin which are probably extracted from the circulating blood, although to a lesser degree they may be derived from hemorrhages into the angioma. The lipid and to a lesser extent the hemosiderin are contained within phagocytic endothelial cells. Aggregations of endothelial

PLATE VI



Capillary Hemangioma

In addition to formation of new vessels there is marked proliferation of endothelial cells.



cells may fuse to form foreign body giant cells. The tumors of the skin containing large amounts of blood pigment are often mistaken for melanomas. The granules of pigment are larger and more irregular in size and shape than the small, rounded and more uniform melanin granules. They are stained an intense blue by the Berlin blue method. It is possible that some dermatofibromas may begin as sclerosing hemangiomas.

**CAVERNOUS ANGIOMA.**—This form is less common. It has the same structure as erectile tissue, being composed of large blood-spaces or sinusoids lined by endothelium. The commonest site is the liver, where it forms a small dark-red tumor which is discovered accidentally at autopsy. These tumors in the liver may be multiple, but they seldom become large. I have seen, however, a huge angioma which occupied the greater part of the left lobe of the liver. Being unrecognized it ruptured at operation, and the patient died on the table in the course of a few minutes. The cavernous angioma occurs in other positions, *e. g.*, lips, subcutaneous tissue, and muscle. It is not encapsulated, and may infiltrate the surrounding tissue like a malignant tumor. In rare cases metastases are formed in the lungs.

**Lymphangioma.**—This is much less common than a hemangioma. Like the hemangioma it is congenital. It may be localized or diffuse. The vessels may be small or cavernous, and they contain lymph instead of blood, so that the tumor lacks the characteristic color of the hemangioma. Lymphangioma of the tongue causes a diffuse enlargement, known as *macroglossia* (big tongue); a similar swelling of the lip is *macrocheilia* (big lip). *Cystic hygroma* is a large soft swelling in the neck of children which may be mistaken for a cold abscess. More rarely it occurs in the axilla or the side of the thorax. It may be present at birth and tends to become smaller or disappear as the child grows up.

## TUMORS OF HEMOPOIETIC TISSUE, LYMPHOBLASTOMA

This group includes tumors of the lymphoid tissue and bone-marrow. The principal members of the group are lymphosarcoma, reticulum-cell sarcoma, Hodgkin's disease, leukemia, and multiple myeloma. Although these various conditions may be regarded as neoplastic diseases, it is possible that leukemia is not a true tumor, and probable that Hodgkin's disease is not. They arise in blood-forming organs, and will be considered in connection with diseases of these organs.

## NERVOUS-TISSUE TUMORS

Although the central nervous system is ectodermal in origin, it becomes divided into parenchymatous tissue (nerve cells and fibers) and supporting tissue (neuroglia). Tumors of the parenchymatous tissue are very rare, tumors of the neuroglia are very common.

The two important tumors are glioma and neuroblastoma. *Gliomas* constitute the important group of brain tumors and are considered in

connection with diseases of the nervous system. Neuroblastoma is a tumor of neuroblasts, usually occurring in the adrenal medulla, but occasionally in connection with other parts of the sympathetic nervous system. It is described in the section on Diseases of the Adrenal Glands.

**Retinoblastoma.** This tumor has been called glioma of the retina, neuroblastoma, and neuro-epithelioma. It is composed of cells which

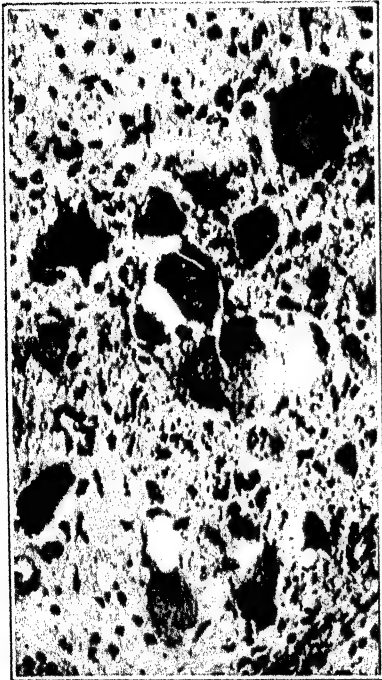


FIG. 145.—Ganglioneuroma.  $\times 300$ .

**GANGLIONEUROMA.** A very rare tumor composed of adult nerve cells and fibers. (Fig. 145.) It is commoner in peripheral ganglia than in the central nervous system. The condition is benign.

started from the anlage of the retina in the embryo and were not developed into functioning cells. It seems best, therefore, to use the term retinoblastoma. It is an uncommon tumor, and presents three striking clinical characteristics: (1) it is bilateral in at least 20 per cent of the cases; (2) over 90 per cent of the cases occur before the fourth year, in this resembling neuroblastoma of the adrenal; (3) it shows an extraordinary familial tendency. In a family of 16 children 10 died of retinoblastoma. The tumor is locally destructive, but later it may form metastases in the lymph nodes and internal organs. *Microscopically* it is composed of small round cells with practically no cytoplasm and no fibrils. The chief characteristic is the presence of circles or "rosettes" of columnar cells, which, however, may be absent. They probably represent inclusions of cells which normally develop into rods and cones.

## EPITHELIAL TUMORS

Epithelial tumors like epithelial cells present certain features which distinguish them from connective tissue cells and tumors. The cells lie in apposition with one another to form groups. The groups are separated from each other by connective tissue, giving what is called an alveolar arrangement, but there is no connective tissue between the cells of the alveolus. The benign epithelial tumors are the papilloma and adenoma, the malignant is the carcinoma.

### BENIGN EPITHELIAL TUMORS

**Papilloma.**—A papilloma is a benign epithelial tumor in which the cells cover finger-like processes of stroma. It grows from a surface, either inter-

nal or external. The term is usually not applied to malignant tumors when they grow in this way, but sometimes it is (malignant papilloma). A papilloma may become malignant, but this is only common in one or two situations, *e. g.*, bladder and rectum. Papillomata may be squamous or mucous, depending on whether they grow from a squamous or mucous surface.

**SQUAMOUS PAPILLOMA.**—This tumor is commonest in the skin, (Fig. 146) but may occur in the mouth, larynx, and any other cavity lined by stratified epithelium. The base may be narrow or broad.

A true papilloma shows proliferation of the squamous epithelium. The epidermis may be thickened and blunt processes may project down into the corium. The term *acanthosis* is applied to a proliferation of the cells of the Malpighian layer, whether neoplastic or otherwise, whilst



FIG. 146.—Squamous papilloma growing from skin.  $\times 7$ .

*hyperkeratosis* signifies thickening of the stratum corneum. The so-called *plantar wart* is a flat papilloma with excessive epidermal thickening and very marked cornification of the surface layers. The thickened epithelium presses on the sensory nerve endings and causes pain on pressure just as does a corn. A corn is simply an excessive surface cornification. Every papilloma has a fibrous core, and in some cases there seems to be more overgrowth of fibrous tissue than of epithelium, which may be of normal thickness.

**MUCOUS PAPILLOMA.**—This is commonest in the large intestine and bladder, but it may grow from any mucous membrane. In the stomach, intestine, etc., a papilloma is commonly called a polypus. Such a polypus is really more of an adenoma than a papilloma, for it is composed of proliferated glands. Gastro-intestinal polypi are often multiple, and in the large bowel there may be hundreds. Mucous polypi in the large intestine and bladder are of great importance because they show a marked tendency to malignant change. (Fig. 147.)

**Adenoma.**—An adenoma is an innocent epithelial tumor of glandular structure which closely approximates that of the gland from which it arises. Unfortunately the matter is not quite so simple as it sounds. Many



FIG. 147.—Mucous papilloma of large bowel. A malignant change had occurred in adjacent part of the tumor.  $\times 60$ .

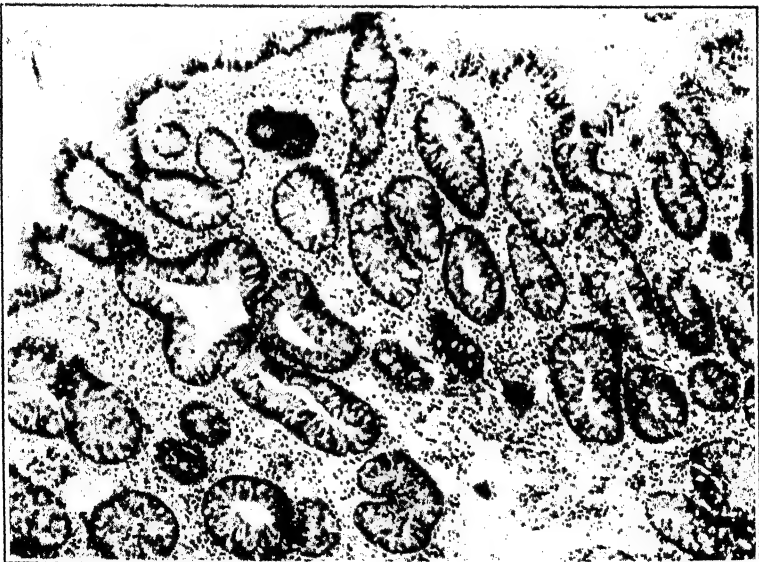


FIG. 148.—Adenoma of rectum. The new glandular acini are quite regular.  $\times 90$

so-called adenomas are not true tumors, but merely examples of localized compensatory hyperplasia. When a portion of the liver is destroyed a mass of new tissue is formed which may project on the surface and be mistaken for an adenoma. A true adenoma is encapsulated, but it is doubtful if the common encapsulated glandular nodules in the thyroid commonly called adenomas are really true tumors. Again an adenoma of the breast may contain more fibrous tissue than epithelium; such a tumor is a fibroadenoma rather than a pure adenoma.

No general description of an adenoma is possible. It is a circumscribed encapsulated nodule which may resemble the gland from which it arises so closely that the microscopic picture of the two may be identical. It consists of gland-like spaces (breast, stomach, bowel, pancreas), or solid cords (liver, adrenal). The glands may be lined by more than one layer of cells, but the acini are perfectly regular, and there is no invasion of the deeper tissue. (Fig. 148.)

In the stomach and large intestine the adenoma commonly develops a stalk owing to contractions of the muscular wall, so that it hangs into the lumen as a polypus. Such a polypus is often called a papilloma, but polypoid adenoma or adenomatous polypus is a more correct name. The frequent development of malignancy in the adenomas of the large bowel has already been alluded to.

The secretion of the cells lining the glandular spaces of an adenoma may lead to distention of these spaces with the formation of cysts. Such a condition is called a cystadenoma. It is best seen in the ovary, where the cysts are lined by tall columnar epithelium which secretes a mucoid material. The cells lining such cysts may become flattened from pressure, or they may proliferate and project as papillary processes into the cysts, a condition known as papillary cystadenoma.

## CARCINOMA

A carcinoma is a malignant epithelial tumor which tends to invade the lymph spaces of the surrounding connective tissue. It is the commonest of all malignant tumors, very much commoner than sarcoma. The cells show the characteristic epithelial arrangement; they are collected into groups or alveoli, with fibrous stroma between the groups but not between the cells of the group. The stroma varies greatly in amount, and largely determines the physical character of the tumor. When the primary tumor is sectioned it may appear to be made up of a large number of separate masses. These are really extensions of the central mass which on section give a fictitious appearance of multiplicity. A wax model would reveal the essential continuity of the tumor.

SPREAD.—Carcinoma may extend in four different ways. (1) *Invasion of the tissue spaces.* This is the fundamental method of spread. The words cancer and carcinoma mean a crab, and these extensions are the claws of the animal. (2) *Lymphatic permeation.* The cancer cells invade the lymphatics and grow along them. (Fig. 149.) Spread along perineural lymphatics is of importance in some tumors, particularly carcinoma of the prostate. (3) By *lymphatic embolism* tumor cells are carried to the regional

lymph nodes and sometimes to more distant nodes. The nearer nodes may also be reached by permeation. (4) *Blood spread* carries the tumor cells to distant organs.

Carcinoma spreads primarily by the lymph spaces and lymphatic vessels. Lymph node involvement is therefore the rule. (Fig. 150.) A lymph node may contain cancer cells and may yet appear normal to the naked eye and show no enlargement, a point of great surgical importance. Suspected early involvement of lymph nodes may be attacked by radiation.



FIG. 149.—Lymphatic permeation by carcinoma.  $\times 125$ .



FIG. 150.—Glandular cancer in lymph node.  $\times 150$ .

As the process becomes more advanced the gland is enlarged, and the cut surface shows a small opaque white nodule. Later the entire gland is occupied by the tumor. In that form of cancer known as squamous-cell or epidermoid carcinoma of the skin, tongue, etc., spread is almost entirely by the lymphatics, although in the last stages the blood vessels may be invaded.

Spread by the blood stream is common, though not nearly so common as lymph spread. (Fig. 151.) In cancer of the gastro-intestinal canal and pancreas the tumor emboli are carried by the portal vein to the liver to form metastases. In carcinoma of other organs (breast, etc.) the lung is the commonest seat of secondary growths. The bones are frequently the site of metastases in carcinoma of the prostate, breast, lung, kidney (hyper-

nephroma) and thyroid. Skeletal metastases may occasionally occur from other carcinomas.

**Squamous-cell Carcinoma.**—This is usually called *epidermoid carcinoma* and used to be known as *epithelioma*. It occurs wherever squamous or transitional epithelium is found, particularly in skin, mouth, tongue, larynx, cervix uteri, and urinary bladder. Epidermoid carcinoma may develop in the edge of a chronic ulcer which refuses to heal. In rare cases it may arise from epithelium which has been changed from the columnar to the squamous stratified type owing to an irritation metaplasia. This is seen in the gall-bladder and in a bronchiectatic cavity in the lung. Most of the skin cancers are on the face and neck; the lower lip is the commonest site. They develop at a point where there has been chronic irritation (fissure, ulcer, local thickening). The tumor begins as a slight thickening or small nodule. At this stage the disease is easily curable. Later an ulcer forms which refuses to heal; the edges are characteristically thickened and indurated. Epidermoid carcinoma spreads by the lymphatics, so that the regional lymph nodes become infected and enlarged. Blood spread is unusual, and only occurs late in the disease.

**Microscopic Appearance.**—Columns of epithelial cells grow down into the dermis. (Fig. 152.) The growth is therefore the reverse of that seen in papilloma. The lower parts of the columns often appear as masses separated from the rest of the growth by the obliquity of the section. In the center of these masses the same process of cornification goes on as occurs

normally on the surface. Granules appear in the cytoplasm, and the cells become converted into hyaline structureless masses of keratin which stain brightly with eosin and are identical with the horny material on the surface of the skin. Such a general picture is well named an epidermoid carcinoma. The cornified masses are known as *cell nests* or *epithelial pearls*. The outer cells of the pearls are often arranged in a concentric manner. The unchanged cells show the "prickle-cell" appearance characteristic of epidermal carcinoma. Cell nests and cornification are absent in rapidly-growing tumors, as they are a sign of differentiation. They are best seen in skin



FIG. 151.—Metastasis from carcinoma of lung in glomerulus and renal tubules.  $\times 175$ .

cancers; sometimes they are found in cancer of the tongue and esophagus, but they seldom occur in cancer of the bladder or cancer of the cervix. The down-growing masses are often surrounded by masses of lymphocytes, especially in tumors of low grade.

**Basal-cell Carcinoma.** This tumor, usually known as rodent ulcer, is a variety of epidermoid carcinoma which is confined to the skin. It is therefore described in Chapter 35.

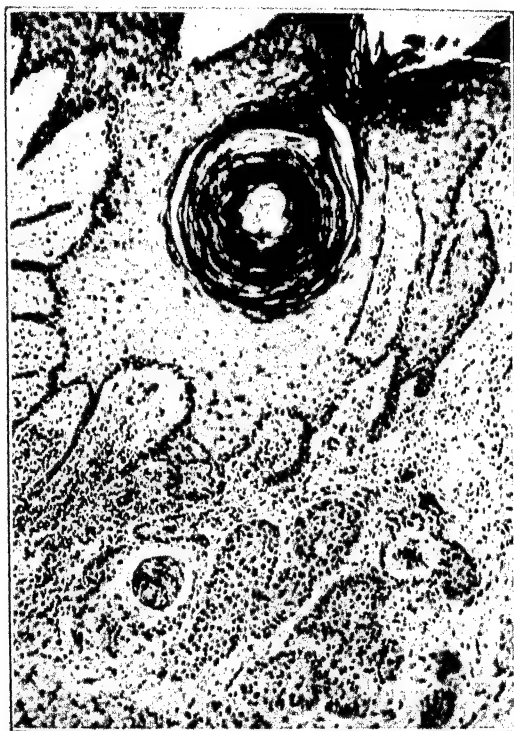


FIG. 152.—Epidermoid carcinoma. Epithelial down-growths into dermis and formation of cell nests.  $\times 60$ .

**Lympho-epithelioma.**—A cancer of distinctive individuality, both clinical and pathological, grows from the epithelium covering lymphoid tissues in the mouth and pharynx, *i. e.*, tonsil, wall of pharynx, nasal passages, and nasopharyngeal sinuses, in which areas the epithelium tends to be transitional between squamous and simple. Its chief characteristic is that the primary growth remains small and often undetected, whereas early dissemination gives rise to marked enlargement of the glands of the neck. The correct diagnosis of these nasopharyngeal tumors is often missed for a long time. Visceral involvement (lungs, liver) may occur at a later date. *Microscopically* the cells are large and pale with indefinite outlines, and are arranged in sheets. There is usually a marked intermingling of epithelial cells and lymphocytes derived from the underlying lymphoid tissue. (Fig. 153.) When the tumor is purely epithelial in type it is referred to as



*transitional-cell carcinoma.* Mitoses are numerous. There may be a tendency toward differentiation with squamous characters appearing, or toward anaplasia so that the tumor in the lymph nodes may be mistaken for a lymphosarcoma. The tumor is markedly radiosensitive, in distinction to epidermoid carcinoma, and is more suitably treated by radiation than by surgery. In essence it is an anaplastic carcinoma of the throat.

**Adenocarcinoma.**—This is a columnar-cell carcinoma with formation of glandular spaces. The common sites are the stomach, large intestine, gallbladder, pancreas, uterus, and prostate. It may occur in the breast and other glandular organs. Spread occurs both by the lymphatics and the blood stream. The gastro-intestinal tumors usually form bulky masses which project into the lumen, but they may be sessile or infiltrating. The change from the normal mucous membrane of the bowel to the irregular glands of the tumor is very sudden. The neoplastic glands are highly atypical with branching processes and darkly-staining cells which contrast strongly with the pale mucinous cells of the normal glands. (Fig. 154). The lining cells are several layers in depth, and are not limited by the basement membrane, but invade the surrounding tissue. Mitoses are numerous. Most characteristic of all, new glands are found in abnormal positions, *e. g.*, deep to the muscularis mucosæ. Sometimes, particularly in the stomach, the glandular formation is lost, and the tumor assumes a scirrhous form with abundant stroma.

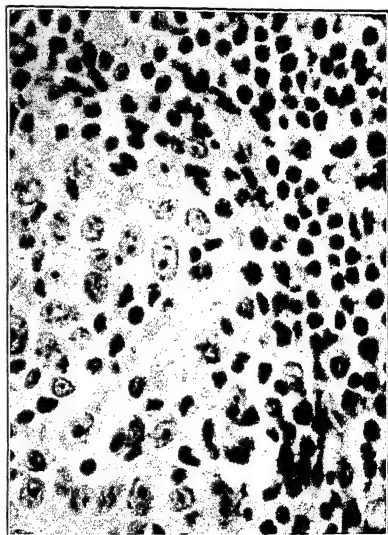


FIG. 153.—Lympho-epithelioma showing intermingling of epithelial and lymphoid cells.  $\times 340$ .

*Mucoid carcinoma*, formerly called colloid carcinoma, occurs principally in the large bowel, stomach, breast and bronchi. Two different forms may be distinguished: (1) primary mucoid carcinoma arising as a tumor of mucus-secreting cells; (2) a secondary form which is merely a mucoid degeneration of a preëxisting adenocarcinoma. Only 15 per cent of cases belong to the true primary form, which is characterized by bulky gelatinous masses, loss of glandular arrangement (also seen in the metastases), large signet-ring cells showing abundant evidence of proliferation, and a high mortality. Many of the cells are greatly distended with mucin (Fig. 155), and large numbers of them disappear completely. In the secondary form the glandular arrangement is preserved with mucus in the acini (Fig. 156), the picture is one of advanced degeneration with little evidence of proliferation, and the malignancy is roughly proportional to the degree of mucus formation.

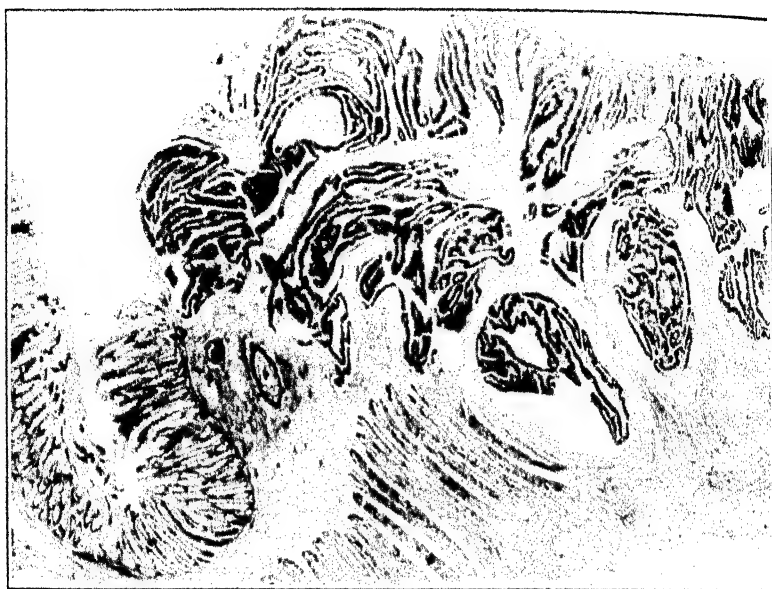


FIG. 154.—Adenocarcinoma, showing the sudden change from normal mucosa to dark, irregular, infiltrating gland spaces on the right.  $\times 10$ .



FIG. 155.—Mucoid carcinoma. The tumor cells are greatly distended with mucin.  $\times 150$ .



FIG. 156.—Secondary form of mucoid carcinoma.  $\times 200$ .

**Carcinoma Simplex.**—Although this term is not commonly used, it is convenient for the purpose of classification, and includes the well-known scirrhous and medullary forms. As a rule, it grows from the cubical epithelium of solid glands. The common site is the breast, just as the common site of squamous-cell carcinoma is the skin and the cervix, and the common site of adenocarcinoma is the stomach. Spread is principally by the lymphatics, but also by the blood stream. The cells are spheroidal or polyhedral, and are arranged in solid masses or columns. In *scirrhous carcinoma* the stroma is dense, the cell groups are small and often present a single column of cells, and the cells are compressed and stain darkly. (Fig. 157.) Mitotic figures are not numerous, for the tumor is not of rapid

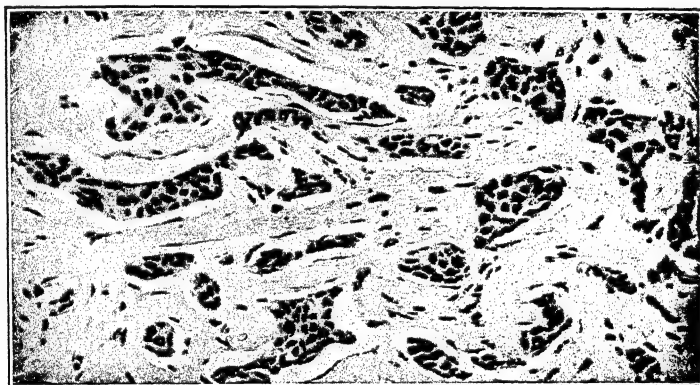


FIG. 157.—Scirrhous carcinoma of the breast. The compressed groups of tumor cells are separated by a dense stroma.  $\times 175$ .

growth. The dense stroma makes the tumor very hard. Most cancers of the breast are of the scirrhous type.

In the *medullary* or *encephaloid* form of carcinoma simplex the proportion of cells to stroma is reversed. (Fig. 158.) The cells are collected in large masses, are actively growing, and show many mitotic figures. The stroma is scanty, so that the tumor is soft (encephaloid). Degeneration and necrosis is common. As one part of a tumor may show a scirrhous picture under the microscope and another a medullary picture, and as the primary tumor may be scirrhous while the metastases may be medullary, it is evident that the distinction between the two forms is in no way fundamental.

**ADAMANTINOMA.**—This is a rare epithelial tumor of the jaw which is one variety of *odontoma*. There are various views as to its origin, but it seems probable that it arises from the group of embryonal cells which comprise the outer epithelial layer of the enamel organ (Zegarelli), so that it may be called an *enameloblastoma*. It is composed of masses of epithelial cells which may become hollowed so as to give a glandular or cystic appearance. There is no constant microscopic picture. The cell type is the basal cell, but there may be all degrees of differentiation of the enamel organ. When differentiation is marked there may be an outer palisade layer of columnar cells, the enameloblasts, and a central core of "star cells" with large vacuoles and connecting cytoplasmic bridges. (Fig. 159.) Or there may be

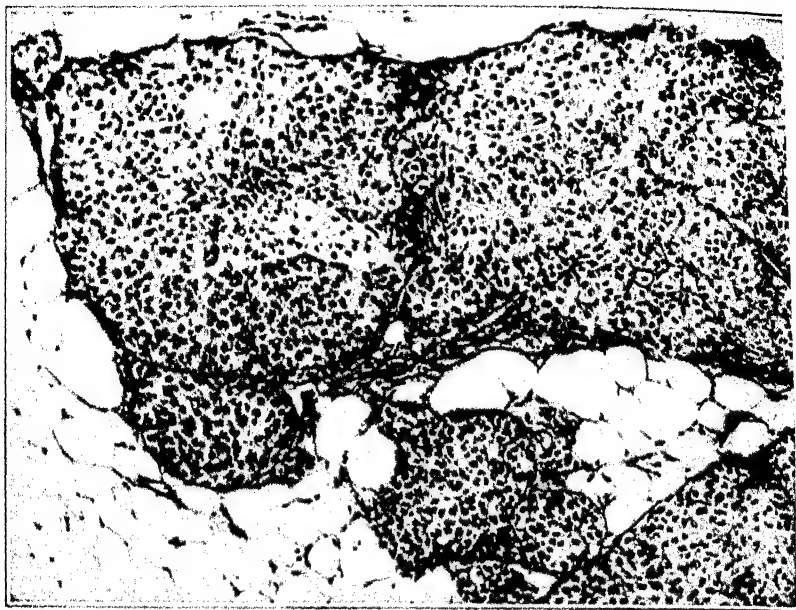


FIG. 158.—Medullary carcinoma of breast, highly cellular.  $\times 110$ .

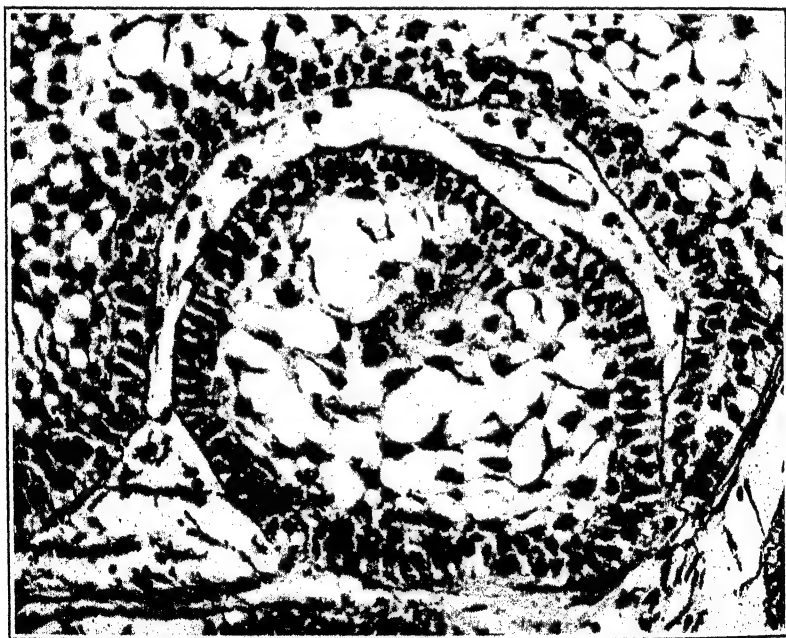


FIG. 159.—Adamantinoma showing palisade of enameloblasts and vacuolated cell  
 $\times 220$ .

strands of epithelium of epidermoid type which branch and form a fantastic network. The undifferentiated forms consist entirely of basal cells. The tumor grows slowly and causes expansion of the jaw until a mere shell of bone is left. Cyst formation may occur. The tumor is usually innocent, but there may be invasion and, in rare cases, metastases.

Similar tumors are found in the stalk of the pituitary, where they are known as suprasellar tumors, and in the tibia. The pituitary stalk arises as an invagination of the oral epithelium, and as the enamel organ has a similar origin it is easy to understand why epithelial cells which retain their embryonic character should give rise to similar tumors in two different sites. The very rare tumors of the tibia are more of a puzzle, but may possibly be explained on a basis of abnormal embryonic epithelial invaginations.

## TERATOMA

A teratoma is a composite mass derived from more than one germinal layer. In some there are representatives of all three layers. It is not a tumor in the strict sense of the word, but rather an attempted formation of a new individual within the tissues of the patient. A malignant growth may develop in a teratoma and may be carcinomatous or sarcomatous in type.

Every grade of complexity may be met with in a teratoma. At one end of the series is the parasitic fetus, an acardiac monster attached to a normal child. Or a jumbled mass of structures may be attached externally either to the upper jaw (*epignathus*) or in the sacral region (*sacral teratoma*). Or again such a mass may develop within the body, usually in the genital glands. The structure may be simpler, comprising only one or two tissues as in the embryoma (teratoma) of the kidney. Finally there may be inclusions of the surface (inclusion dermoids), which may cause tumor-like swellings.

In the early stage of the developing and segmenting ovum the first blastomeres are totipotent; they have the capacity of forming a new individual as shown by the occasional development of identical twins from the one ovum. The later blastomeres are multipotent, *i. e.*, they can form all of the three germinal layers. In the segmenting ovum primitive sex cells (germinal cells) are separated from the somatic cells and migrate finally to the testicle and ovary, where they develop into spermatozoa or ova. Theoretically it is quite possible for one of the primitive germ cells to be segregated either in the sex glands or in some other part of the body, where, if it could be stimulated to divide, it may form a teratoma which is an abortive attempt at the production of a new individual even to the extent of forming chorionic membranes, for the chorionic epithelium is merely a modification of the fetal ectoderm. A blastomere may also be segregated, and if it is stimulated to grow it will form structures derived from the three germinal layers, a confused jumble of tissues, but not including fetal membranes. MacCallum suggests that the teratomas may be divided into two main classes, the first representing the development of a primitive *germinal* cell, the second being derived from a segregated *somatic* blastomere. These two forms belong to different generations, the first being analogous to a true offspring, the second to a twin brother.

Jacques Loeb, as is well known, succeeded in inducing parthenogenesis in the unfertilized ova of sea-urchins and even frogs by employing various physical and chemical stimuli. The resulting animals were apparently normal except that they possessed no sex cells. In 1926 Bosaeus published an account of some extraordinarily interesting experiments on the parthenogenetic formation of teratomas. He removed an ovum from a frog's ovary, pricked it with a needle, and reimplanted the stimulated ovum into the body of the same frog. As the result of parthenogenesis a teratoma developed which was similar in type to some of the teratomas

occurring in man. When the ovum was placed in the body of another frog it failed to develop.

A new possibility is provided by advances in experimental embryology. It is now known that differentiation depends on two factors: (1) chemical organizers, (2) susceptibility or "competence" of the cells to the action of the organizers. Both of these change as development proceeds. Thus there are primary, secondary and tertiary organizers, and the susceptibility of the cells alters with the course of development. When there is perfect balance between organizers and susceptibility, differentiation proceeds normally, but if organizers are produced too abundantly or too early or if susceptibility persists beyond the period at which it is normally lost, the result may be uncontrolled differentiation with the production of a jumble of structures so characteristic of teratomas.



FIG. 160.—Choroid plexus in teratoma (chorione epithelioma) of testicle.  $\times 175$ .

Perhaps the most varied structures are encountered in teratomas of the genital gland. In the dermoid cyst of the ovary are found skin, hair, sebaceous material, teeth, bone, brain, thyroid, etc. In teratoma of the testicle, glands, cartilage, muscle, brain, and even choroid plexus may occur (Fig. 160).

**INCLUSION DERMIDS.** Although these have the same name as the congenital tumors occurring in the genital glands, their origin is quite different. They may be divided into congenital and implantation dermoids; in both cases there is inclusion of dermal and epidermal structures.

*Congenital Dermoids.* Congenital dermoids are inclusions of dermal tissue along the line of the embryonic fissures. Dermal tissue, it may be with hair and cyst formation, is found in the middle line of the abdomen and chest (mediastinal dermoid), in the skull (line of attachment of dura mater to tentorium cerebelli), in the line of the thyroglossal duct and the duct leading from pharynx to pituitary, and at the site of the branchial clefts, particularly the second.

*Implantation Dermoids.*—Implantation dermoids are the result of a

small piece of skin being implanted in the deeper tissues, usually as the result of trauma with a pointed instrument. A small cyst lined by epidermis is formed. These cysts are most common on the hands of manual laborers.

#### ADDITIONAL READING

**Adamantinoma.** BUMP: Surg., Gynec., and Obst., 1927, **44**, 173. KEGEL: Arch. Surg., 1932, **25**, 498. ZEGARELLI: Am. J. Path., 1944, **20**, 23.

- Adamantinoma of Tibia.** DOCKERTY AND MEYERDING: *J. A. M. A.*, 1942, **119**, 932.
- Benign Epithelial Invasion.** BOYD: *Canad. Med. Assn. J.*, 1934, **31** 273. WHITE AND WEIDMAN: *J. A. M. A.*, 1927, **88**, 1959.
- Biopsies.** HELWIG: *Arch. Path.*, 1932, **13**, 607.
- Cancer and Ageing.** SAXTON *et al.*: *Arch. Path.*, 1950, **50**, 813.
- Causes of Cancer.** RHOADS: *Rev. Gastroenterol.*, 1952, **19**, 217. BITTNER: *Cancer Research*, 1952, **12**, 387.
- Carcinoma in Situ.** BRODERS: *J. A. M. A.*, 1932, **99**, 1670.
- Chordoma.** CAPPELL: *J. Path. and Bact.*, 1928, **31**, 797. CONGDON: *Am. J. Path.*, 1952, **28**, 793.
- Cytological Diagnosis of Cancer.** HUNTER AND RICHARDSON: *Surg., Gyn. & Obst.*, 1947, **85**, 275. MAGNER: *Canad. M. A. J.*, 1950, **63**, 103. PANICO *et al.*: *J. A. M. A.*, 1950, **143**, 1308. TAYLOR & THOMPSON: *Canad. M. A. J.*, 1949, **61**, 413.
- Cytology of Cancer.** FIDLER: *Am. J. Cancer*, 1935, **25**, 772. MACCARTY: *J. Cancer Res.*, 1929, **13**, 167.
- Dermatofibroma.** STECKER AND ROBINSON: *Arch. Dermat. Syph.*, 1941, **43**, 498.
- Environmental Cancer.** HUEFER: *Environmental and Occupational Cancer. U.S. Public Health Reports*, 1948, Supplement 209.
- Etiology of Tumors.** BITTNER: *Am. J. Cancer*, 1937, **30**, 530. BITTNER AND LITTLE: *J. Hered.*, 1937, **28**, 117. COOK, *et al.*: *Am. J. Cancer*, 1937, **29**, 219. DUNLAP, *et al.*: *Am. J. Path.*, 1944, **20**, 1. EGGERS: *Arch. Path.*, 1931, **12**, 983; 1932, **13**, 112. GREENE: *J. Exper. Med.*, 1939, **70**, 147, 159; *Science*, 1945, **101**, 644. KOLETSEY and GUSTAFSON: *Am. J. Path.*, 1953, **29**, 606. LOEB: *J. A. M. A.*, 1935, **104**, 1597. LUCKE: *Am. J. Cancer*, 1934, **20**, 352. NEEDHAM: *Biochemistry and Morphogenesis*, Cambridge, 1942. ROUS: *Am. J. Cancer*, 1936, **28**, 233; *J. A. M. A.*, 1943, **122**, 573. SHOPE: *J. Exper. Med.*, 1933, **58**, 607. SUGIURA AND RHOADS: *Cancer Research*, 1941, **1**, 3. WOLBACH: *Am. J. Path.*, 1937, **13**, 662.
- Experimental Cancer.** BIELSCHOWSKY: *Brit. J. Exper. Path.*, 1944, **25**, 1, 90. COOK, *et al.*: *Am. J. Cancer*, 1937, **29**, 219. COPELAND AND SALMON: *Am. J. Path.*, 1946, **22**, 1059. DES LIGNERIS: *Am. J. Cancer*, 1940, **39**, 489. EARLE: *J. Nat. Cancer Inst.*, 1943, **3**, 555. EARLE AND VOEGTLIN: *Am. J. Cancer*, 1938, **34**, 373. KLEINENBERG, *et al.*: *Am. J. Cancer*, 1940, **39**, 463. PASSEY, *et al.*: *J. Path. and Bact.*, 1935, **40**, 198. YAMAGIWA AND ICHIKAWA: *J. Cancer Res.*, 1918, **3**, 1.
- Fibrosarcoma.** STOUT: *Cancer*, 1948, **1**, 30.
- General References.** BORST: *Die Lehre von den Geschwülsten*, Wiesbaden, 1902; *Echte Geschwülste*, in Aschoff's *Pathologische Anatomie*. Jena, 1921, vol. 1. EWING: *Neoplastic Diseases*, Philadelphia, 1940; KETTLE: *The Pathology of Tumors*, London, 1925. RIBBERT: *Geschwülstlehre*, Bonn, 1914. SROUT: *Human Cancer*, Philadelphia, 1932. WILLIS: *The Pathology of Tumors*, Butterworth & Co. Ltd., London, 1952.
- Glomangioma.** BAILEY: *Am. J. Path.*, 1935, **11**, 915. MASSON AND GERY: *Ann. d'anat. path.*, 1927, **4**, 153. MURRAY AND STOUT: *Am. J. Path.*, 1942, **18**, 183. POPOFF: *Arch. Path.*, 1934, **18**, 295. Stout: *Am. J. Cancer*, 1935, **24**, 255.
- Grading of Tumors.** BRODERS: *Arch. Path.*, 1926, **2**, 376. v. HANSEMAN: *Die mikroskopische Diagnose der bosartigen Geschwülste*, Berlin, 1902. REIMANN: *Arch. Path.*, 1929, **8**, 803.
- Hemangiomas, Sclerosing.** GROSS AND WOLBACH: *Am. J. Path.*, 1943, **19**, 533.
- Heredity in Tumors.** CHAMPLIN: *J. A. M. A.*, 1930, **95**, 96. LITTLE: *J. A. M. A.*, 1936, **106**, 2234. MACKLIN: *Canad. Med. Assn. J.*, 1932, **27**, 182. SLYE: *J. Cancer Res.*, 1927, **11**, 135. WARTHIN: *J. Cancer Res.*, 1928, **12**, 249. WELLER: *Am. J. Cancer*, 1937, **30**, 39.
- Industrial Cancer.** HUEFER: *Occupational Tumors and Allied Diseases*, Springfield, 1942.
- Intra-epithelial Carcinoma.** DUNN: *J. Path. and Bact.*, 1930, **33**, 297. MUIR: *Brit. Med. J.*, 1930, **2**, 587.
- Liposarcoma.** EWING: *Arch. Surg.*, 1935, **31**, 507. GESCHICKTER: *Am. J. Cancer*, 1934, **21**, 617. MORELAND AND McNAMARA: *Arch. Surg.*, 1942, **45**, 164.
- Lymphoblastoma.** CALLENDER: *Am. J. Path.*, 1934, **10**, 443.
- Melanoma.** ALLEN: *Cancer*, 1949, **2**, 28. BERKEHEISER AND RAPPOPORT: *Am. J. Path.*, 1952, **28**, 477. DAWSON: *Edinburgh Med. J.*, 1925, **32**, 509. FOOT: *Am. J.*

- Path., 1932, 8, 309, 321. LAIDLAW: Am. J. Path., 1932, 8, 477; 1933, 9, 827. LUND & STROMER: Am. J. Path., 1949, 25, 1117. NYSSON: Ann. d'anat. path., 1926, 3, 117. NYSSON: Cancer, 1951, 4, 9. Ann. d'anat. path., 1926, 3, 117. SPITZ: Am. J. Path., 1948, 24, 591.
- Metabolism of Tumors.** WARRING: The Metabolism of Tumors, London, 1930. GOLDBLATT and CAMERON: Jour. Exp. Med., 1953, 97, 525.
- Multiple Tumors.** MURRAY: Lancet, 1927, 2, 800.
- Myoblastoma.** AMBROKOSOFF: Virchow's Arch. f. path. Anat., 1926, 260, 215. CRANE and TREMBLAY: Am. J. Path., 1945, 21, 357. FOST AND CUSTER: Am. J. Path., 1948, 24, 671. Am. J. Clin. Path., 1949, 19, 522. GRAY and GREENFELD: Am. J. Cancer, 1937, 30, 699. HOWE and WARREN, SHIELDS: Surgery, 1944, 16, 319. KLEMPERER: Am. J. Cancer, 1934, 20, 324.
- Neurogenic Sarcoma.** QUICK and CUTLER: Ann. Surg., 1927, 86, 810. STEWART: Am. J. Cancer, 1934, 15, 1235.
- Organizers and Carcinogenesis.** WADDINGTON: Nature, 1935, 135, 606.
- Prognosis in Cancer.** MCCORMICK: Canad. M. A. J., 1946, 55, 460.
- Radiation and Cancer.** CAGLE: Malignant Disease and its Treatment by Radium, Bristol, 1940. GLUCKSMANN: Brit. J. Radiol., 1948, 21, 559; 1952, 25, 38. PATERSON: The Treatment of Malignant Disease by Radium and X-rays, London, 1948. WARREN *et al.*: Arch. Path., 1942, 34, 443, 562 & 749. WARREN *et al.*: Am. J. Clin. Path., 1952, 22, 411. MARTLAND: Am. J. Cancer, 1931, 15, 2435. ROSS: J. Path. and Bact., 1932, 35, 899; 1936, 43, 267. WARREN: Physiol. Rev., 1944, 24, 225. CATHIE: J. Path. and Bact., 1939.
- Relation of Cancer to Occupation.** HUEPER: Occupational Tumors and Allied Diseases, Springfield, Ill., 1942.
- Rodent Ulcer.** MOLESWORTH: Med. J. Australia, 1927, 1, 878.
- Spontaneous Cure of Cancer.** GREENE and LUND: Cancer Research, 1944, 4, 352.
- Spread of Tumors.** RYSON: Ann. Int. Med., 1942, 16, 38; Ann. Surg., 1940, 112, 138. BLACK *et al.*: Am. J. Path., 1953, 29, 505. BRANDES, *et al.*: Surg., Gyn. and Obstet., 1946, 82, 212. BURROWS: Arch. Int. Med., 1926, 37, 453. EISENBERG: Am. J. Path., 1949, 25, 802. GILCHRIST: Ann. Surg., 1940, 111, 630. GRAY: Brit. J. Surg., 1939, 26, 162. OERTER: J. Path. and Bact., 1935, 40, 323. SAPHIR: Am. J. Path., 1947, 23, 245. WALTER: Krebsmetastasen, Basel, 1948. WARREN and MAYER: Am. J. Path., 1938, 14, 605. WILLES: The Spread of Tumors in the Human Body, London, 1952. ZEIDMAN and BUSSE: Am. J. Path., 1952, 28, 533. ZEIDMAN, McCUTCHEON and COWAN: Cancer Research, 1950, 10, 357.
- Teratoma.** MACCALLUM: Textbook of Pathology, Philadelphia, 1932, Chap. 72. WILLES: J. Path. and Bact., 1935, 40, 1.
- Transplantation of Tumors.** GREEN and WHITELEY: Brit. Med. J., 1952, 2, 538. HOCH-LIGETI and HSU: Science, 1953, 117, 360. TOOLAN: Cancer Research, 1953, 13, 389.
- Trauma and Tumors.** BEHAN: Relation of Trauma to New Growths, Baltimore, 1939. EWING: Arch. Path., 1935, 19, 690. KNOX: Arch. Path., 1929, 7, 274. MACKENZIE and ROUS: J. Exper. Med., 1941, 73, 391. PULLINGER: J. Path. and Bact., 1943, 55, 301. WARREN: Ann. Surg., 1943, 117, 585.
- Xanthoma.** PLEWES: Arch. Path., 1934, 17, 177.



## Chapter

# 11

## VITAMIN DEFICIENCY

AVITAMINOSIS or insufficiency of vitamins may be a manifestation of *primary* malnutrition caused by dietary inadequacy; even the so-called bland diet of a hospital regimen may lead to vitamin deficiency. Much malnutrition, however, is *secondary* to disease. There may be interference with absorption from the bowel due to intestinal lesions. Diffuse disease of the liver such as cirrhosis may diminish the storage capacity of the liver. Fever, hyperthyroidism and pregnancy may accelerate metabolism and thus increase the nutritional requirements of the body. Even glucose solution given over a period of several days will wash out the reservoirs of thiamine, and may lead to the development of acute symptoms such as severe vomiting and paralytic ileus.

Although intensive investigation has been carried on with regard to individual vitamins, it must be remembered that malnutrition is often not the result of absence of any one vitamin, that the administration of a single vitamin in a chemically pure state may not serve to correct the condition, and that no laboratory mixture is the equal of a good well-balanced diet. Moreover it is not possible to keep an animal alive on a vitamin-free diet to which has been added all the pure vitamins known.

**VITAMIN A.**—Vitamin A as such occurs in bright yellow animal foods such as butter and the yolk of eggs. Various plants such as corn and sweet potatoes contain precursors of the vitamin which are converted into active vitamin A by animal tissues. Being fat-soluble, it is stored in the fat of animals, and it is present in greatest abundance in cod-liver oil (although much is lost in the process of refining), but fresh milk contains an adequate supply for the growing child, especially when combined with yolk of eggs. Moore has shown that animals can synthesize it in the liver from the vegetable pigment carotene, so that it may be given directly as cod-liver oil or indirectly as vegetables. The conversion takes place in the liver through the action of an enzyme. The vitamin has been isolated in chemically pure form, and has been synthesized.

Vitamin A gives a green fluorescence in ultra-violet light, which disappears rapidly. Popper points out that similar fluorescence, presumably due to vitamin A, can be seen in frozen sections of certain tissues. It is most marked in the liver, adrenal cortex, and corpus luteum. In hypervitaminosis A the amount is increased.

The basic lesion of vitamin A deficiency is atrophy of columnar epithelium and a substitution of stratified keratinizing epithelium due to proliferation of the basal cells, *i. e.*, a keratinizing metaplasia, which may be regarded as an attempt at repair following atrophy (Wolbach). In the human infant this occurs in the conjunctiva, nasal mucosa, accessory nasal sinuses, salivary glands, trachea, bronchi, pancreas, renal pelvis.

ureters, and uterms. The commonest and earliest change is in the trachea and bronchi, and death is often due to pneumonia. The lumen of the ducts is blocked by desquamated keratinized cells so that cysts are formed in glands, bronchiectatic cavities in the lungs, etc. In the eye a late effect is *xerophthalmia*. The cornea dries up (*xero*, dry) and becomes ulcerated and infected. This is due to involvement of the lacrimal glands, as a result of which the tears are no longer produced and the cornea is not bathed with fluid as it should be. Mellanby suggests that the corneal lesion may be due to loss of the neurotrophic control of the cornea by the ophthalmic division of the trigeminal nerve, for degeneration of the myelin sheath of that nerve develops at the same time as the corneal degeneration, and in early cases both lesions are recovered from as the result of adding vitamin A to the diet. The salivary glands also become dried up. Xerophthalmia is rarely seen in Europe and America, but in Japan and other eastern countries poorly-nourished children not infrequently develop the condition. Vitamin A may share with other essential factors certain anti-infective properties. To refer to vitamin A as an "anti-infection vitamin" is now probably misleading.

Animals on a diet deficient in vitamin A may develop *degenerative lesions in the posterior and lateral columns of the spinal cord*. These are very similar to the lesions (combined degeneration) often seen in the cord in severe cases of pernicious anemia. It is possible that there are two dietetic factors in the production of the advanced picture of pernicious anemia: (1) a water-soluble factor concerned with the formation of the red blood cells, and (2) a fat-soluble factor absence of which leads to degeneration in the central nervous system.

*Night-blindness* (hemeralopia, more correctly nyctalopia) has long been known to be benefited by cod-liver oil. Hippocrates recommended ox liver dipped in honey for a cure, and in Newfoundland cod's liver is a popular remedy. Any source of vitamin A will effect a cure. Night-blindness is due to exhaustion of the visual purple after prolonged exposure to brilliant sunlight, and lack of vitamin A interferes with regeneration of the visual purple.

**VITAMIN D.** Much of the romance of the vitamins centers around this member of the group. Being fat-soluble it was at first confused with vitamin A, which is also fat-soluble. Milk, butter, egg-yolk, and other fats contain vitamin D, but far the most abundant supply is cod-liver oil. The vitamin has been obtained chemically pure. It has the same chemical formula as ergosterol,  $C_{27}H_{44}OH$ , and appears to be an isomer of that substance, being formed from it as the result of the action of ultra-violet light. Irradiated ergosterol is known as vitamin  $D_2$ , and on account of its cheapness it is used in most fortified food preparations.

*Vitamin D controls calcium metabolism.* Whether or not it acts in conjunction with the parathyroids is uncertain; probably not. The vitamin has two fundamental and independent actions: (1) to increase the absorption of calcium from the gastro-intestinal canal, and (2) to increase the excretion of phosphorus in the urine. When the vitamin is deficient or absent from the diet there is great interference with calcification and *rickets* results. What is actually interfered with is the calcification of the proliferat-

ing cartilage at the epiphyses. This must be distinguished from true ossification which consists in the replacement of the calcified cartilage by true bone and bone-marrow. The complex subject of rickets and the several etiological factors involved will be discussed in connection with the diseases of bones, and will therefore not be considered here.

The work of May Mellanby has shown what an important influence vitamin D has on the *development of the teeth* both in the experimental animal and in the child. When the diet contains an abundance of vitamin D (milk, egg-yolk, etc.), the teeth are even, bright, shiny, and well formed. With a diet poor in vitamin D, especially if it is rich in cereals, the teeth are uneven, poorly calcified, dull, and discolored. *Caries* is a disease of poorly developed and poorly calcified teeth, but there is no general agreement as to the relationship between avitaminosis and the development of human caries.

The possibility of *hypervitaminosis* deserves mention, although there is no danger of this with ordinary therapeutic doses. When large overdoses of vitamin D (irradiated ergosterol) are given there is hypercalcemia and hyperphosphatemia. If the diet is deficient in calcium there is removal of calcium from the bones. If, on the other hand, the diet is rich in calcium the bones are much less affected, but there are calcareous deposits in many of the tissues, being most marked in the renal tubules and the walls of the arteries. Renal insufficiency favors calcification of the soft tissues, for it interferes with the excretion of phosphorus, and high serum phosphorus is even more important than high serum calcium in promoting calcification of soft parts.

**VITAMIN B.**—Vitamin B, one of the water-soluble vitamins, is a complex substance containing a number of components; for that reason the term vitamin B complex has come into use. The complex may be defined as the collection of vitamins present in the yeast cell. New factors are continually being separated, but from the standpoint of pathology the four most important are thiamine, riboflavin, niacin and folic acid. This group of vitamins is one of the most widely distributed, being present in all natural foodstuffs, but much of it is lost in the process of refining and of converting natural foods into artificial foods, as in the case of white bread, polished rice, etc.

*Thiamin* or  $B_1$  is the antineuritic vitamin. It is the heat-labile component of the complex, and is an essential factor in enzyme systems concerned with carbohydrate metabolism. When rice is polished the skin and the embryo are removed, and it is these which contain the vitamin. Birds fed on polished rice develop an avitaminosis known as the polyneuritis of birds or rice disease. This is characterized by extreme ataxia followed by paresis due to peripheral neuritis, together with anemia, lymphopenia, and hyperglycemia. In experimental observations on pigs, Follis and his associates found focal and diffuse myocardial necrosis associated with marked cardiac dilatation in animals dying of thiamin deficiency. Thiamin deficiency is involved in the neuritis recurring in chronic alcoholism, pregnancy and diabetes. Its most striking manifestation is beri-beri, although this is certainly not an example of pure vitamin  $B_1$  deficiency. Milder forms of thiamin deficiency, which may be due to the use of a diet composed largely of white bread, are not uncommon. They are characterized by symptoms suggesting myocardial disease, such as tachycardia, dyspnea, edema, and enlargement of the heart. These may be associated with numbness and tingling of the hands and feet.

*Riboflavin* or  $B_2$  plays an important part in normal tissue respiration. Mild forms of ariboflavinosis are not uncommon among the undernourished and those who subsist on absurdly inadequate diets with the object of improving their figure. Severe eye lesions are seen not only in the southern states of America, but also

throughout the world, particularly in large cities. This condition has been eliminated in areas adopting successful nutritional programs, particularly the enrichment of bread and flour with  $B_1$ ,  $B_2$  and niacin. There may be cheilosis (fissured lesions at the corners of the mouth), erosions around the eyes, and rough desquamation of the sides of the nose. The most serious disturbances are those involving the eye. In those whose occupation exposes them to bright light (including workers with the microscope) there may be photophobia, eye fatigue, redness of the conjunctiva and lower lids. The earliest and most common sign is circumcorneal injection, best revealed by the slit lamp. In more advanced cases there is invasion of the cornea by capillaries arising from the limbic plexus with final corneal opacity and keratitis.

*Niacin* or nicotinic acid is necessary for normal tissue oxidation. It is known as the P-P or pellagra-preventing factor, and is of great value in treating the major symptoms of pellagra, although that disease is not an example of a pure avitaminosis but is apparently due to multiple nutritional deficiencies. *Pellagra* is a disease of maize-eating countries (Italy, the southern United States, etc.), but is not confined to these regions. There is a curiously symmetrical pigmentation and erythema followed by desquamation of the exposed parts of the body (face and back of hands), gastro-intestinal disturbance, and finally nervous and mental disorders. Muscular weakness is marked. The chief microscopic lesions of the skin are a severe grade of hyperkeratosis in the epidermis and edema and congestion in the dermis, with some round-cell infiltration in the superficial layers of the dermis.

Gillman and Gillman, by means of repeated liver puncture on South African negroes suffering from pellagra, have shown that fundamentally important changes take place in the liver in the course of the disease. The first change is extensive fatty degeneration. This is followed by a massive accumulation of iron pigment in the liver cells, necrosis of these cells, and finally cirrhosis. This of course is the picture of hemochromatosis. According to Gillman and Gillman 20 per cent of pellagrins in South Africa show evidence of incipient or frank cirrhosis of the liver.

*Vitamin B<sub>12</sub>* and *folic acid* are growth factors in the maturation of red blood cells in the bone marrow.  $B_{12}$  is formed by the action of an enzyme of gastric juice on a food protein. In the absence of  $B_{12}$  pernicious anemia develops. It is, therefore, known as the anti-pernicious anemia principle, and it is the chief agent of liver extracts used in the treatment of that disease. Folic acid being another maturation principle is also used in the treatment of pernicious anemia. Its disadvantage is that it does not prevent involvement of the central nervous system, which is prevented by  $B_{12}$ . Failure of growth in children is benefitted by  $B_{12}$ , which is also a growth factor for bacteria in unbelievably minute amounts.

**BERI-BERI.**—Beri-beri is a disease of eastern countries due to eating polished rice. The principal features are peripheral neuritis, edema, and myocardial weakness, a triad of symptoms which is found in no other disease. The disease differs in some respects from the experimental rice disease of birds. In both there is polyn neuritis, but the birds do not show the edema and cardiac failure, while the beri-beri patients do not show the anemia, lymphopenia, and hyperglycemia characteristic of the experimental disease. Vitamin deficiency is an essential factor in the production of beri-beri, but it is rarely so complete as to be the sole agent, and it is probable that the addition of an infection is needed to give the classical picture.

Among the autopsy findings are edema of the legs, fluid in the serous sacs, and marked enlargement (both hypertrophy and dilatation) of the right side of the heart. In addition there is marked degeneration of the peripheral nerves (Wallerian degeneration) and degenerative changes in

the motor nerve cells of the anterior horn of the spinal cord and of the sensory nerve cells in the posterior root ganglia.

A form of pellagra may occur as the result of chronic gastro-intestinal disease. The patients show the characteristic gauntlet or glove dermatitis, but the other signs are not so marked as in the edemic form. Among the conditions which have given rise to this form of deficiency disease are extensive cancer of the stomach, postoperative obstructive lesions of the small bowel, and inflammation and cancer of the colon.

**VITAMIN C.**—The other water-soluble vitamin is the antiscorbutic one. Vitamin C is present in all fresh fruits and vegetables, being particularly abundant in tomato, orange, lemon, and grape-fruit. It is present in smaller amount in fresh meat and milk. Steffanson maintained himself in the Arctic on a diet of fresh meat alone without developing scurvy. The vitamin is easily destroyed by heat, so that boiled or pasteurized milk may be completely lacking in it. It is the duration of heating rather than the actual temperature which seems to matter. The drying of fruits also destroys the vitamin.

Vitamin C is identical with an hexuronic acid (ascorbic acid), isolated in crystalline form from adrenal cortex as well as fruit juices. It can be demonstrated in the gross by an intense blackening produced by silver nitrate on exposure to light. The adrenal cortex in scurvy is depleted of fat and cholesterol as well as of vitamin C. In scurvy the level of ascorbic acid is low in the urine and very low in the blood. In health the tissues should be saturated with the vitamin, and when the dye 2:6-dichlorophenolindophenol is injected intradermally it is discolored. This does not occur when the vitamin is deficient.

**SCURVY (SCORBUTUS).**—Scurvy is the result of a deficiency of vitamin C in the food. Once the scourge of sailors and explorers who were unable to carry supplies of fresh fruit and vegetables, it is now seldom seen in the adult since it was found that lime juice would act as an excellent preventive. The reason for the prophylactic power of the lime juice is, of course, a modern discovery. In war, in beleaguered cities, etc., scurvy may still prove a menace. In some countries the potato is the chief antiscorbutic article of diet during the winter months. In such a country as Ireland a potato famine has often been accompanied by an outbreak of scurvy. But it is in children that the disease is most likely to be seen at the present day, for modern methods tend to destroy the vitamin in the child's natural food. Scurvy is practically never met with in breast-fed children. But it may develop in bottle-fed babies, for the sterilization of the milk (boiling or pasteurization) destroys the antiscorbutic vitamin. Even keeping the milk instead of using it fresh lessens the vitamin content. The addition of orange juice to sterilized milk restores to the full its antiscorbutic power.

The obvious *lesions of scurvy* are hemorrhages and changes in the bones. But the essential underlying lesion is an inability of the supporting tissues to produce and maintain intercellular substances. The effect is on cells of mesenchymal origin in contrast to the ectodermal and endodermal effects of vitamin A deficiency. The intercellular substances concerned are the collagen of all fibrous tissues, the matrix of bone, dentine and cartilage, and all non-epithelial cement substance including that of vascular endothelium. The weakening of the capillary walls is responsible for the hemorrhage which forms so prominent a feature of the disease. There may be

hemorrhages in the skin, mucous membranes, muscles, lungs, nerve sheaths, under the periosteum, and into the joints. Hemorrhage in the adrenals is one of the earliest changes in experimental scurvy. The gums are soft, spongy, and bleed readily and the teeth may fall out. If the teeth are bad, the mouth and breath become very foul. Bone formation is brought to a standstill, and as the normal process of bone absorption still goes on the bones become rarefied and fragile. The formation of the cartilaginous and bony matrix ceases, the osteoblasts become elongated, assume the shape of fibroblasts, proliferate, and accumulate between the bone and periosteum, forming a thick cellular layer devoid of matrix into which massive hemorrhages occur. Characteristic lesions are seen at the epiphyseal line. The normal narrow line of ossification is broadened and dense, giving a pathognomonic picture in the roentgen-ray film. Fragments of bone are scattered about, and hemorrhages are frequent. It is not a disturbance of calcification as in rickets, but of ossification. When a proper diet is given, osteogenesis is rapidly resumed.

*Infantile Scurvy (Barlow's Disease).*—Infantile scurvy is similar to adult scurvy, but the symptoms due to the bone lesions dominate the picture. The legs are so tender that the child screams if they are even touched. This tenderness is due to subperiosteal hemorrhages. Growth of the bones is naturally in abeyance. The gums may be tender and bleeding. The disease usually appears in the second half of the first year. After the second year it is seldom seen in an acute form as the diet is more varied, but there may be minor manifestations which are often unrecognized.

**VITAMIN E.**—This is the antisterility vitamin and belongs to the fat-soluble group. It is present in growing things, and is especially abundant in the wheat germ, but is contained in sufficient quantity in lettuce, meat, whole wheat and other foods. Deficiency of the vitamin produces different lesions in the two sexes. In the male the spermatozoa are destroyed, and there is finally degeneration of the entire seminiferous epithelium. In the female the ovaries do not appear to be injured, fertilization of the ovum occurs, and gestation commences, but about the eighth day in the rat pathological changes set in, in the placenta and the fetus dies and is absorbed. In addition to its effect on the reproductive function, vitamin E is a necessary factor for the preservation of the integrity of skeletal muscle. When female mice are maintained on a vitamin E low diet but are given a single dose of vitamin to ensure the birth of living young, the offspring show marked necrosis of skeletal muscle in 20 per cent of cases with early calcification (Pappenheimer).

**VITAMIN K.**—In 1930 Dam, of Copenhagen, noticed that chicks fed on a deficient diet developed hemorrhages owing to the loss of coagulating power of the blood, and that this was prevented by giving alfalfa. The coagulation factor in the alfalfa was extracted, crystallized and finally synthesized. It was called Koagulations-vitamin or vitamin K. The vitamin is necessary for the manufacture of prothrombin, so that when the vitamin is deficient the prothrombin in the blood is low. Estimation of the plasma prothrombin thus affords a simple method of determining if there is deficiency of vitamin K. Such deficiency in man is probably never due to lack of the vitamin in the food. It does occur in obstructive jaundice and in hemorrhagic disease of the newborn. Unless bile is present in the bowel vitamin K is not absorbed, prothrombin is not formed in sufficient amount, and hemorrhage occurs. In *obstructive jaundice* bile is prevented from entering the bowel. This explains the marked tendency to bleeding after operations on jaundiced patients. The bleeding can be prevented by the administration of bile and vitamin K, or by giving the synthetic vitamin by mouth (the synthetic product is absorbed without the assist-

ance of bile), or intravenously. If the liver is severely damaged (cirrhosis, amyloid, etc.) the administration of vitamin K is of no avail, because it is in the liver that the prothrombin is produced which is essential to coagulation. The explanation of *bleeding in the newborn* is that vitamin K is produced by the action of intestinal bacteria, and these are absent during the first few days of life. At birth the baby has sufficient prothrombin from the maternal blood, but this rapidly falls, and there may be severe and even fatal hemorrhage, particularly intracranial. This can be prevented by giving the mother vitamin K before delivery.

Most of the work on the vitamins has consisted of devising special food mixtures and inducing in experimental animals such striking pictures as those of scurvy, rickets, and beri-beri. It is probable that in man, particularly in children, many minor disturbances may be due to deficiencies in diet. The reader is referred to McCarrison's very interesting book for a discussion of this matter. McCarrison is of the opinion that much of the gastro-intestinal disorder so common at the present day is to be attributed to a deficient and ill-balanced diet. He says that the health of the alimentary canal is dependent on vitamins B and C, that lack of B gives rise to changes like colitis, while lack of C causes congestion and hemorrhages of the bowel even though the patient never develops the classical manifestations of scurvy. He shows that many of the organs atrophy in deficiency disease, but that in all of the deficiencies there is a remarkable enlargement of the adrenals.

The laboratory worker concentrates on producing a single deficiency in the experimental animal. In man many of the deficiency diseases are multiple deficiencies, for dietary deficiency is rarely confined to a single factor, at least in this country. For this reason the administration of pure vitamins is rarely sufficient for a cure, and is never a substitute for a good general diet. In 1939 over \$86,000,000 were spent by the United States public in buying vitamins. It is better and infinitely cheaper to get one's vitamins from the grocery store, where they have been manufactured by Nature, than from the drug store where they have been manufactured by man.

## ADDITIONAL READING

- Calcification in Hypervitaminosis D.** OPPER: Arch. Path., 1941, 31, 569.  
**Pellagra.** GILLMAN AND GILLMAN: Arch. Path., 1945, 40, 239. SODEMAN: Am. J. Med. Sci., 1938, 196, 122.  
**Riboflavin Deficiency.** SYDENSTRICKER, *et al.*: J. A. M. A., 1940, 114, 2437.  
**Tissue Changes in Vitamin Deficiencies.** WOLBACH AND BESSEY: Physiol. Rev., 1942, 22, 233.  
**Vitamin A.** MELLANBY: J. A. M. A., 1931, 96, 325; J. Path. and Bact., 1934, 38, 391. MOORE: Biochem. J., 1930, 24, 692. POPPER: Arch. Path., 1941, 31, 766. POPPER AND GREENBERG: Arch. Path., 1941, 32, 11. WOLBACH AND HOWE: Arch. Path., 1928, 5, 239.  
**Vitamin B.** FOLLIS, *et al.*: Am. J. Path., 1943, 19, 341. GYÖRGY AND GOLDBLATT: J. Exper. Med., 1940, 72, 1. ZIMMERMAN AND BURACK: Arch. Path., 1932, 13, 207.  
**Vitamine C.** HESS: Scurvy Past and Present, Philadelphia, 1920. WOLBACH AND HOWE: Arch. Path., 1926, 1, 1.  
**Vitamin D.** GOUGH, *et al.*: Brit. J. Exper. Path., 1933, 14, 137. MELLANBY AND PATTISON: Brit. Med. J., 1932, 1, 507. SCHLUTZ: J. A. M. A., 1932, 99, 384.  
**Vitamin E.** PAPPENHEIMER: Am. J. Path., 1942, 18, 169.

## INJURIES CAUSED BY PHYSICAL IRRITANTS

## HEAT

**Burns.** The effects of a burn depend on two quite different factors: (1) its severity, and (2) its extent. An extensive burn of moderate severity may be as serious as a severe but localized burn. There are three degrees of severity. The *first degree* indicates damage to the epidermis with hyperemia and vesication, the *second degree* involves dermis as well as epidermis with varying amounts of damage to sebaceous and sweat glands and their hair follicles, whilst in the *third degree* the entire thickness of the skin is destroyed.

The *systemic effects* of severe burns are very important, and there is much difference of opinion as to their explanation. When the burn covers a large surface the patient may die within twenty-four hours of shock—at least the symptoms are the same as those of traumatic shock. If death does not take place within that period a series of apparently *toxic symptoms* develop, such as delirium, vomiting, bloody diarrhea and circulatory failure. In experimental burns immediate removal of the burned area prevents the onset of these symptoms, and if the burned area is transplanted into a normal animal the symptoms will appear in that animal. Such facts suggest that some at least of the symptoms are due to the absorption of toxins from the burnt surface, but there is no agreement as to the nature of the toxin. Histamine may be liberated and may be responsible for the shock. A deep but limited burn may be shut off from the general circulation by local thrombosis, so that general toxic symptoms fail to develop.

Another factor which may be of even greater importance is concentration of the blood, which rapidly occurs in superficial burns owing to a great outpouring of fluid through the damaged capillaries into the subcutaneous tissue. (Fig. 161.) This sudden local edema may lead to a remarkable concentration of the blood as shown by hemoglobin estimation (Underhill), and this leads in turn to circulatory failure and oxygen starvation of the tissues. The hemoconcentration sends up the red cell count, sometimes as high as 8,000,000. These features are, of course, those of shock. It is probable that the hemoconcentration is due to general as well as local loss of fluid. Such loss is the essence of the shock syndrome, and may be attributed to toxic action on capillary endothelium throughout the body increasing its permeability. Ham has shown by experiments on the skin of the young hog that when only the superficial layer of dermis is involved tanning of the skin by means of tannic acid prevents fluid loss from the superficial plexus of vessels which are normally concerned in temperature



regulation. In deeper burns there is no such effect, because the fluid loss is from vessels which cannot be reached by the tanning process.

Autopsy on the early cases shows little beyond congestion of the brain and meninges. At a slightly later stage the autopsy picture of shock may be presented, *i. e.*, congestion, edema and hemorrhage in the viscera, especially the lungs, and fluid in the serous cavities. After about the third day lesions may appear which for want of a better word may be called toxicemic. Cloudy swelling is marked in the liver, kidney, etc. Necrosis of



FIG. 161



FIG. 162

FIG. 161.—Severe burn of skin showing great edema and thrombosed vessel.  $\times 175$ .

FIG. 162.—Necrosis of liver in a case of burns treated with tannic acid.  $\times 120$ .

the liver is often found in fatal cases by the third or fourth day, most marked in the central and mid-zone areas. This necrosis may be extremely severe, so that the picture may actually resemble that of yellow atrophy of the liver. (Fig. 162.) Mitoses are common and intranuclear inclusions like those of yellow fever may be present (Belt). These lesions have become noteworthy since tannic acid became the accepted treatment of burns. Wells and his associates have produced identical and fatal lesions by the subcutaneous injection of tannic acid. It seems probable that the hepatic necrosis is due to the tannic acid treatment, which for long has been a favorite method of dealing with burns. It is not a characteristic lesion of

fatal cases not treated with tannic acid (Baker). The matter is complicated by the fact that tannic acid tides the patient with burns over the first few critical days, and it is only after this interval that the liver lesions either of burns or tannic acid become apparent. In the Hospital for Sick Children, Toronto, careful autopsy examination on tanned and untanned cases of burns showed liver necrosis in 61 per cent of the tanned cases, whereas no liver necrosis occurred in the untanned group (Erb, Morgan and Farmer). I have seen bilateral necrosis of the renal cortex due to thrombosis. A large amount of blood pigment may be deposited in the kidney, particularly in the straight tubules. The adrenals are much swollen, deep red in color, and show numerous hemorrhages. Hemorrhages are present under the endocardium and epicardium. Acute duodenal ulcers occasionally develop, perhaps due to the action of toxins absorbed, perhaps to emboli.

**HEAT STROKE.** This is essentially a paralysis of the heat-regulating mechanism caused by exposure to excessive heat. The actual temperature required depends on the humidity and varies with different persons. Heat loss is largely regulated by sweating, and some people can perspire very little. Complete saturation of the air with water vapor when the temperature is 90° F. causes an uncontrollable rise of body temperature. When the air temperature exceeds the body temperature all loss of heat by radiation ceases, and regulation of temperature is entirely dependent on sweating. A distinction is often drawn between heat exhaustion and heat stroke. It is doubtful if they differ other than in degree. In *heat exhaustion* the heat-regulating mechanism is severely strained, and the patient manifests weakness, pallor, stupor, and low blood-pressure. The temperature may be slightly raised, but on the other hand it may be subnormal. In *heat stroke* the heat-regulating mechanism is overwhelmed, and the temperature may rise 10° or more. One case is on record in which the temperature reached 117° F. It should be noted that the rectal temperature may be much higher than the temperature in the mouth or the axilla.

Heat stroke may be caused by direct exposure to the sun, the condition known as sun stroke. The ultra-violet rays have no relation to the condition. But the same effect is produced by exposure to any great heat, especially when combined with marked humidity. Men in steel works, engine rooms, etc., often suffer in this way.

In the condition of heat stroke the patient may die with startling suddenness. He may fall down unconscious, a condition known as *heat apoplexy*, not uncommon in soldiers on forced marches in tropical countries. Even in the less sudden cases the patient may soon become unconscious. In heat exhaustion the skin may be moist, but in heat stroke it is usually dry and burning; the patient appears unable to perspire. The temperature may rise to great heights, but not in every case.

The *pathological lesions* are very indefinite. The chief autopsy findings are petechial hemorrhages in the skin and mucous membranes, hyperemia or actual hemorrhages in the brain, cerebral and pulmonary edema, enlargement of the spleen, and cloudy swelling of the liver, kidneys and heart. The water content of the brain is high. Patients with a temperature of 110° F. have recovered, but such a temperature can only be endured for a short time, for it has been shown experimentally that a temperature of 108° F. if long continued will cause coagulation of the globulin of the nerve cells. After death from heat stroke the body shows very rapid and very marked rigor mortis. Postmortem decomposition also sets in very quickly.

## COLD

**DEATH FROM FREEZING.**—When a person inadequately protected is exposed to severe and long-continued cold, the blood is driven from the surface into the interior of the body. The temperature gradually falls, metabolism slows down, and the patient is overcome by the irresistible and fatal desire to sleep, so well known to mountaineers caught by bad weather at high altitudes. When the temperature reaches 70° F. the heart stops.

**Frostbite.**—The action of extreme cold on exposed parts of the body (nose, ears, hands, and even feet), especially when combined with the rapid loss of heat caused by wind, is to produce frostbite. As in the case of burns there are various degrees. In mild frostbite the part, which is at first white and bloodless, becomes red, swollen, and very painful during the process of thawing out. In more marked cases there is some necrosis of the epidermis, with formation of blisters and subsequent desquamation. In the severe cases there is necrosis of the entire part and gangrene. If the cold is sufficiently great the fluid of the cells is crystallized, and the cells are torn to pieces by the ice crystals. In ordinary cases the major factor in the production of the gangrene is the ischemia due to extreme contraction of the blood vessels, together with damage to the capillaries with the formation of hyaline thrombi.

An important element in the production of ischemia and anoxia is the process of *stasis*, which occurs quite early in frostbite (Kreyberg). As a result of severe injury to the vessel wall there is exudation of the fluid elements of the blood, so that the red cells become agglutinated into a jelly-like column which blocks the lumen effectively with resulting necrosis. This condition is known as sludging of the blood. The process is reversible if treatment be not delayed too long, even though the tissues have been frozen solid. The word *stasis* is here used in the Continental sense, rather than in its usual connotation of slowing of the blood stream.

High altitude frostbite in aviators presents a special problem. In an airplane at great altitude the face can be exposed to severe cold for several hours, but under similar conditions the fingers suffer to such an extent that gangrene may result. Intense reflex vasospasm of the peripheral arterioles causes ischemia and local anoxia. The constriction, which is almost instantaneous, occurs chiefly at the terminal end of the arterioles. This is followed by damage to the endothelium of the terminal capillary loops, with increased permeability of the loops or thrombosis at the arteriolar-capillary junction. If extravasation of fluid occurs before thrombosis the hand may become dropsical owing to accumulation of fluid between dermis and epidermis, or blistering may occur. In cases where amputation of the fingers has been necessary later the arteries may show a remarkable fibrous thickening of the intima apparently unrelated to previous thrombosis.

## LIGHT

Light is a form of energy and may act as an irritant just as does heat. It is made up of vibrations of very varying wave length. The shorter the wave length the less

is the penetrating power and the more are the rays arrested in the skin where they excite irritation. The rays beyond the short wave end of the visible spectrum (ultra-violet) create most irritation, while those beyond the long wave end (infra-red) are most penetrating and cause least irritation. Light may affect the body in the following ways:

1. Ultra-violet light produces the condition known as *sunburn*. This is independent of heat, for climbers on high snow peaks may be severely burned. The greater the altitude the more severe is the effect, for the short wave rays are no longer filtered out by a thick layer of atmosphere. Direct sunlight is not necessary, for the most severe burn I have ever experienced was on a day of thick mist in the Alps. The sensitivity of the skin varies much in different persons, depending on the amount of melanin it contains. Blondes burn much more readily than brunettes. The process of tanning (not burning) consists in a deposition of melanin in the more superficial layers.

The pathology of sunburn is the same as that of a first degree burn. There is intense hyperemia, a varying degree of edema, and some emigration of leucocytes. The edema may be so great as to raise the skin in blisters. Marked desquamation may follow the burn.

2. Those whose occupation exposes them for long periods to bright sunshine, *e. g.*, farmers and sailors past middle age, often develop thickened patches or *keratoses* on the skin of the face and back of the hands. The importance of these keratoses is that not infrequently they form the starting-point of carcinoma.

Probably related to this condition is the rare but remarkably interesting disease known as *xeroderma pigmentosum*. This appears to be a congenital hypersensitivity to the action of light. In young children following prolonged exposure to sunlight there appear patches of erythema which go on to pigmentation. These patches then become rough and scaly, warty elevations appear (keratoses), and many of these become cancerous, so that the disease is usually fatal before the twentieth year. Metastases are rare both in this disease and in carcinoma following senile keratoses. There may be several cases in one family, but it is limited either to the males or the females.

3. A *hypersensitivity to light* may be present. In one of the rare inborn errors of metabolism, hematurporphyria congenita, hematurporphyrin is present in the blood and appears in the urine; the skin is hypersensitive to bright light, developing vesicles. The bones are pigmented. Even more remarkable is the sensitization which follows the experimental injection of hematurporphyrin. When an animal is treated in this way it becomes as sensitive to ordinary white light from which the ultra-violet rays are excluded by red glass as is a normal animal to ultra-violet rays. The hematurporphyrin appears to act as a sensitizer in the photographic sense. When the sensitized tissues are exposed to ordinary light there is a complete stasis in the vessels followed by necrosis. Exposure to intense light is followed by acute general effects, *i. e.*, excitement, convulsions, and death in the course of a short time.

4. Ultra-violet light exerts a *photochemical action on the lipids of the skin*. The cholesterol of the skin seems to be activated by ultra-violet light and converted into vitamin D. Sunlight or the ultra-violet light from a mercury-vapor lamp is as efficacious in the treatment of a vitamin D deficiency disease like rickets as is the administration of cod-liver oil.

## ELECTRICITY

The passage of an electric current through the body may cause burns of varying severity or may result in death; the latter condition is known as electrocution.

The *local effects* are those of a burn. The current enters the body at one spot and leaves it at another. It is at these points where resistance is encountered that evidence of the burn is most marked. At the point of exit the lesion is particularly severe, as in a gunshot wound, the tissues sometimes showing radiating tears. The point of exit is often on the feet, as the current leaves the body there to pass into the ground. The burn may be of any degree of severity. It usually does not look as bad as it really is. At first it is dry and bloodless, but in the course of thirty-six hours marked hyperemia and edema have developed. Little cavities may be found in the epidermis, supposed to be caused by the sudden generation of steam. A slough separates, and the ulcer thus formed is singularly slow to heal, usually taking two or three times as long as in the case of an ordinary burn.

The *general effects* resemble those of any severe burn. In fatal cases the viscera are congested, the serous membranes show petechial hemorrhages, the lungs are edematous, and the right ventricle is full of dark fluid blood. Death is probably due to respiratory rather than to cardiac failure, for the patient may sometimes be resuscitated by prolonged artificial respiration. The muscles are flaccid, although during life they may be in a state of severe tetanic spasm. There may be chromatolysis and degeneration of the nerve cells. The blood vessels are severely injured for they serve as good conductors of the current, so that thrombosis and severe hemorrhages are common. In judicial electrocution the current is applied to the central nervous system and death is instantaneous, so that most of the above changes are not found.

*Lightning* produces the same results. There may be all kinds of skin wounds—puncture wounds, lacerations and bruises. Bands of scorched skin may pass from the point of entry (usually the head) down the body to the point of exit. The most characteristic feature is the so-called current markings or lightning figures, peculiar arborescent red lines on the skin which are probably caused by the current being split up in dendriform fashion within the body.

## ROENTGEN RAYS AND RADIUM

The destructive effect of roentgen rays and radium is identical, so that they may be considered together. The alpha rays and soft beta rays of radium are absorbed in the superficial layers and are therefore destructive to the skin; the hard beta rays and gamma rays penetrate readily and therefore are less likely to burn the skin. The alpha rays are the most potent agent known to science. They are 10,000 times more destructive than the gamma rays owing to the terrific impact of the alpha particle, and we shall see presently what happens when they exert their influence on the interior of the body. Fortunately they are very readily screened out; a thickness of 1 mm. of tissue is sufficient to stop them. Roentgen-ray burns were common in the early days before the importance of screening was understood; they are seldom seen now. The radiations act primarily on the nucleus of the cell, not on the cytoplasm. The normal cell is far more vulnerable during division than in the resting stage; the same is true of tumor cells.

Radioactive isotopes produce effects similar to those of radium and roentgen rays. An isotope is one of two forms of an element which are chemically identical yet differ slightly in atomic weight by virtue of possessing an additional neutron in the nucleus. Thus stable phosphorus is referred to as  $P^{31}$ , whilst radioactive phosphorus is  $P^{32}$ . The effect of radioactive

phosphorus is exerted when an electron or beta particle is emitted from the substance. When this occurs  $P^{32}$  is transformed into ordinary stable sulphur. The activity of the radioactive isotopes is strictly limited in duration. As a result of their chemical affinities they are concentrated in certain tissues (iodine in the thyroid, phosphorus in the hemopoietic tissues), so that their radioactivity will be selective in type.

Radiations may produce a burn of the skin, but this displays some very special features. The lesion does not appear at once, there being a latent period of about two weeks. The changes which then develop are of all degrees of severity. There may only be the usual hyperemia and swelling with falling-out of the hair. Blisters may form, and a necrotic slough may separate leaving an ulcer. The burned skin may become like parchment and may not separate for a considerable time. The burn may include the skin, the subcutaneous fat, and even the muscles. Healing is very slow, and scarring may go on for months, causing marked deformity. At any time fresh ulceration may develop in the affected area. Repair indeed is never complete. It has been well said that a healed roentgen-ray burn is not a cured roentgen-ray burn.

A rather different set of changes is seen as the result of frequent small doses. These frequently developed in the hands of radiologists before efficient screening was practised. Some of the features of roentgen-ray dermatitis are as follows: patches of atrophy in the skin; areas of hyperkeratosis which may come and go, and finally may develop into carcinoma; scaldiness of the skin and painful cracks and fissures; brittleness and splitting of the nails; a dermatitis like xeroderma pigmentosum; the development of telangiectases in the skin. The fingers and hands may be lost.

These effects are due partly to the direct action of the radiations on the tissues, but are largely secondary to the all-important vascular changes. Microscopically there is the usual hyperemia and exudation of inflammation. In cases of long standing the epidermis shows marked signs of proliferation. Many of the cells are undergoing mitosis, and downgrowths of epithelial cells invade the corium. It is in these lesions that carcinoma is apt to develop. There may be an interval of some years between the last exposure and the development of carcinoma, but active processes are going on the whole time. Fibrosis of the corium is marked, and the new fibrous tissue may be extremely dense and acellular. Vascular changes are constant. The capillaries may be dilated and form telangiectases. In the arteries, and to a lesser degree in the veins, there is a remarkable thickening of the subendothelial coat producing extreme narrowing of the lumen and in many cases complete occlusion. It is for this reason that proper healing is impossible and that subsequent breaking-down of the scar is so frequent. Thrombosis is common in the narrowed vessels.

**Atomic Bomb Radiation.**—The radiation effects of an atomic bomb explosion are indistinguishable from the lesions produced by exposure of the whole body to million volt X-radiation (Tullis). The most sensitive elements are lymphoid cells, myeloblasts, erythroblasts, germ cells, and intestinal epithelium. The result of damage to these cells is anemia and lowered resistance to infection. There is general dilatation of capillaries, with impairment of circulation and resulting tissue anoxia. The one bright

spot is that the reticular cells of lymph nodes and bone-marrow—the primitive hematopoietic stem cells—are relatively resistant, so that recovery is theoretically possible under adequate supportive treatment.

**INDUSTRIAL HAZARDS.**—If radio-active substances in the form of salts gain entrance to the body there may be terrible consequences. These substances may be present in infinitesimal amounts, but as they are stored within the body, particularly in bones, their action is cumulative and unceasing. Roentgen-ray pictures have been taken using the bones of a body exhumed five years after death, so rich were they still in radio-active material. Workers with radio-active paints have been exposed to this hazard. Girls employed in painting luminous dials of watches used to lick the brushes many times a day. In this way the radio-active material gained entrance to the body, and the unscreened alpha rays, which are really particles of matter rather than true waves, were free to exert their destructive action. Being stored in the bones they set up a continual bombardment of the bone-marrow, with the result that a profound and fatal leucopenic anemia was produced. In addition both the upper and lower jaws developed destructive lesions like those of phosphorus poisoning, due as in that disease to bacterial infection from the mouth being super-added to a specific osteitis. Once the alpha particles have been introduced into the body it is impossible ever to get rid of them. For this reason the matter is one of great importance from the viewpoint of public health.

## TRAUMA

The commonest of physical irritants is trauma, so common indeed that were the subject to be considered fully it would necessitate a discussion of injuries of every organ in the body. A few of its effects may be considered here. The most readily recognized result of trauma is *bruising*, due to tearing of minute vessels in the subcutaneous or deeper tissues. The resulting extravasation of blood may be diffuse or localized depending on the looseness or density of the tissue. The kaleidoscopic procession of colors in bruising of the tissues is well known; first red, then bluish-green, and finally fading away into yellow, as the hemoglobin is converted into bilirubin and then gradually removed. Signs of inflammation are also present especially when the injury is severe, due to liberation of histamine by the lacerated tissues. If there is great destruction of tissue, the histamine passing into the circulation may produce a condition of shock. There may be *rupture of viscera* such as liver, spleen or bowel. It must be noted that serious internal injuries may be produced without bruising of the skin, even though the trauma be quite severe. Traumatic head injuries, with or without fracture of the skull, are considered in Chapter 31.

Many other instances of the effect of trauma will be encountered in the sections dealing with Special Pathology; the examples given above are merely chosen as characteristic of the varied reactions which it may produce in the tissues.

## INCREASED ATMOSPHERIC PRESSURE

*Caisson disease* or diver's palsy is a result of a sudden alteration in the atmospheric pressure. A caisson is a cylinder containing air under high pressure used for sinking piers in the construction of bridges. Caisson workers, tunnel workers (under rivers), and divers are subjected to high air pressures. If they are "decompressed" too quickly or return to a normal atmosphere too suddenly they develop headache, vertigo, dyspnea, pains all over the body called "the bends," and it may be paralysis. While the person is under high pressure a large amount of air, particularly nitrogen,

is dissolved in the blood plasma. As the result of sudden decompression this gas is released as bubbles in the blood, and these form emboli particularly in the brain and spinal cord. Numerous small infarcts of the central nervous system are produced in this way and are responsible for most of the symptoms. Bubbles of gas may also be liberated in the nervous tissue and cause disintegration.

### ADDITIONAL READING

- Atomic Bomb Injury.** LE ROY: J. A. M. A., 1947, **134**, 1143. LEROW *et al.*: Am. J. Path., 1949, **25**, 853. TULLIS: Am. J. Path., 1949, **25**, 829. TULLIS AND WARREN: J. A. M. A., 1947, **134**, 1155.
- Burns.** BAKER: Am. J. Path., 1945, **21**, 747. BELT: J. Path. and Bact., 1939, **48**, 493. CAMERON, *et al.*: Lancet, 1943, **2**, 179. CHRISTOPHE: La Mort des Brûlés, Paris, 1939. ERM, *et al.*: Ann. Surg., 1943, **117**, 234. HAME: Ann. Surg., 1944, **120**, 698. HARKINS: The Treatment of Burns, Springfield, Ill., 1942. MOON: Shock, its Dynamics, Occurrence and Management, Philadelphia, 1942. PACK: Arch. Path., 1926, **1**, 767. UNDERHILL, *et al.*: Arch. Int. Med., 1923, **32**, 31. WELLS, *et al.*: New England J. Med., 1942, **226**, 629.
- Cold.** BROWN AND HORTON: Trans. Assn. Am. Phys., 1932, **47**, 353. HORTON, *et al.*: J. A. M. A., 1936, **107**, 1263. MUDD, *et al.*: J. Med. Res., 1919, **40**, 53; J. Lab. and Clin. Med., 1921, **6**, 175.
- Electricity.** HELPERN AND STRASSMANN: Am. J. Path., 1944, **17**, 592. JAFFE: Arch. Path., 1928, **5**, 837.
- Frostbite.** BIGELOW: Canad. Med. Assn. J., 1942, **47**, 529. DAVIS, *et al.*: Surg., Gynec. and Obst., 1943, **77**, 561. KREYBERG: Lancet, 1946, **1**, 338. ROTNES AND KREYBERG: Acta path. et microbiol. Scandinav. Supp. 1932, **11**, 162.
- Heat Stroke.** MARSH: Lancet, 1930, **2**, 904. SHOUDY AND BAETJER: Surg., Gynec. and Obst., 1936, **62**, 475.
- Light.** LEVY: J. Path. and Bact., 1929, **32**, 387. MACKEY AND GARROD: Quart. J. Med., 1925-1926, **19**, 357.
- Radiation.** DESJARDINS: Arch. Surg., 1932, **25**, 926. MARTLAND: J. A. M. A., 1929, **92**, 466. WARREN *et al.*: Arch. Path., 1942, **34**, 443, 562, 749.
- Radioactive Isotopes.** PLATT: Arch. Path., 1947, **43**, 1.
- Trauma.** MORITZ: Pathology of Trauma, Philadelphia, 1942.
- Xeroderma Pigmentosum.** COUNCILMAN AND MAGRATH: J. Med. Res., 1909, **21**, 331.



## Chapter

# 13

## INJURIES CAUSED BY CHEMICAL POISONS

THE subject of the action of chemical poisons on the body is a very large one, and is adequately treated in textbooks of toxicology and forensic medicine. For this reason many textbooks of pathology make no reference to the subject, and I considered the advisability of omitting the present chapter. But the medical practitioner may at any time have to perform an autopsy on a case of suspected poisoning, and it is desirable that he be familiar with the pathological findings caused by some of the more common poisons and the precautions which should be observed in collecting the material for chemical analysis.

Poisoning may be suicidal, homicidal or accidental. In a case of suspected poisoning which may assume medico-legal importance extreme care must be taken in performing the autopsy. The external appearances should be noted. Everything should be recorded in writing and nothing left to the memory. The stomach and bowel must be kept. When there is a question of diffusible toxins such as arsenic and strychnine, it is well to keep all the internal organs and much of the muscles. These various specimens are sent to the chemist for chemical analysis. They must be put into clean glass jars, which are then stoppered, sealed, and labelled. No preservative of any kind should be added.

In the description which follows only the commoner and everyday exogenous poisons are discussed. The endogenous poisons produced as the result of abnormal metabolism and bacterial poisons (toxins) are not considered.

**CORROSIVE ACIDS.**—The strong acids most likely to be taken for suicidal purposes are sulphuric, nitric, and hydrochloric. They are similar in action, and produce burns not only in the stomach, but also in the mouth, pharynx, and esophagus. The lesions of the lips must not be overlooked. The stomach is contracted as the result of irritation and thrown into folds. Patches of necrosis are scattered over the folds, and if the patient lives long enough the slough separates and leaves a raw surface. Similar changes are seen with all corrosive poisons. The acids vary as regards the color of the burns. With sulphuric acid the burnt tissue is brownish-red or black, with nitric acid it is yellow, and with hydrochloric acid white. The microscopic appearance is one of necrotic tissue on the surface with intense inflammation of the surrounding tissue. The acid removes water from the cells and dissolves epithelium and connective tissue. Nitric acid poisoning is common in munition works where smokeless powder is made from nitrocellulose obtained by treating cotton with strong nitric acid. If the fumes of the acid are inhaled severe inflammation of the larynx and trachea is produced.

**CAUSTIC ALKALIS.**—The strong alkalis (caustic soda, caustic potash, and lime) are also corrosive in their action. They dehydrate the cells and saponify the fats.

The common form of alkali poisoning is by commercial lye taken either for suicidal purposes or accidentally by children. The lesions are similar to those of the corrosive acids. There is severe burning of the lips, mouth, throat, esophagus, and stomach, with acute inflammation and softening of tissue. Should the patient recover, cicatricial stricture of the esophagus often develops and sometimes stricture of the pylorus.

**CARBOLIC ACID.** Strong carbolic acid is so easily obtained that it is commonly used for suicidal purposes. The picture differs in several ways from that of poisoning by other strong acids. The burns on the lips and in the mouth, throat, and stomach have a peculiar opaque, dead-white appearance. The stomach is contracted, and the dead patches are seen on the summit of the folds. Phenol is not a corrosive acid. It is an excellent fixative, so that the tissue instead of being destroyed is perfectly fixed. It follows that although the gross appearance is so abnormal, the microscopic picture is actually more normal than usual, because the customary postmortem changes in the stomach are absent. If the patient survives for some time the dead tissue will become detached with separation of a slough. The effect of dilute carbolic acid is rather different. The tissue is not killed and fixed so completely, and an intense hemorrhagic inflammation is the result of the irritation. When the stomach is opened in carbolic acid poisoning the characteristic color of phenol can be recognized.

**CORROSIVE SUBLIMATE.** This substance is also a favorite with suicides. When bichloride of mercury is taken in the form of a concentrated solution and in large quantity it fixes the tissue in the same way as does phenol. Grayish-white patches of coagulation necrosis are surrounded by an area of intense inflammation. When, as often happens, tablets are swallowed, they produce severe local necrosis with deep ulceration. After a few days a second set of symptoms develops connected with the colon and the kidney. By whatever route mercury enters the body, through the skin and mucous membrane (vaginal douches) as well as by the mouth, it is excreted into the large bowel, where it produces an intense hemorrhagic colitis. It is also excreted by the kidney. The cells of the convoluted tubules show extensive necrosis, and there is marked suppression of urine and sometimes anuria. In the course of a week or less there occurs an "acute calcification" of the renal lesion, calcium salts being deposited in the masses of necrotic cells, many of which lie free in the lumen of the tubules. This very rapid calcification is a remarkable phenomenon which is difficult to explain.

**ARSENIC.** Arsenical poisoning may be acute or chronic. The acute form is usually suicidal, Paris green, rat poison, etc., being easily obtained. Chronic arsenical poisoning may be homicidal. Many of the famous murders in history have been accomplished by the continued administration of small doses of arsenic. Fashions change, however, and more violent methods are now in vogue. Arsenic is an intense irritant, so that in acute poisoning there is severe hemorrhagic inflammation of the entire gastro-intestinal canal. The poison is excreted into the bowel, giving an enteritis as well as a colitis. Paris green or crystals of arsenic may be seen in the folds of the stomach. In chronic poisoning the lesions are mainly in the skin and the nervous system. There is pigmentation and extreme keratinization of the skin. The nervous changes are mental disorders and paralysis of the peripheral nerves due to neuritis. Arsenical poisoning may be the result of the careless administration of arsphenamine and other arsenical preparations. In these cases the chief changes are optic atrophy with blindness and extensive necrosis of the liver. The latter lesion is often fatal.

**PHOSPHORUS.** This is likely to be taken in the form of rat poison or the phosphorus may be obtained from the heads of matches. Phosphorus poisoning may be acute or chronic. In the *acute form* there is a hemorrhagic inflammation of the stomach. The characteristic smell of phosphorus may be detected when the stomach

is opened. After an interval of some days there is acute necrosis of the liver with a picture of acute yellow atrophy, accompanied by intense jaundice and widespread hemorrhages. Phosphorus is one of the most potent causes of fatty degeneration, and this change is present in marked degree in the liver, kidneys, heart, and even the voluntary muscles. *Chronic poisoning* is due to exposure to phosphorus vapor, and is an occupational disease. Apart from fatty degeneration the chief lesion is necrosis of the jaws (phossy jaw) with destruction of bone and loss of the teeth. The process is dependent on bacterial infection, commencing around the roots of carious teeth. In this and other respects it closely resembles the lesion of industrial radium poisoning.

**LEAD.**—Lead poisoning (plumbism) differs from those already described in being chronic in type; acute lead poisoning is of no importance. It is usually an occupational disease, the lead being inhaled in the form of dust or fumes or absorbed through the skin. White-lead workers and pottery workers are liable, and painters unless they wash their hands well before eating. A severe anemia develops, of which the characteristic feature is an extreme degree of basophilic granular degeneration (stippling) of the red cells. In no other disease is this change so marked. A blue line (lead line) of lead sulphide appears at the junction of the gum and the teeth, owing to the action of sulphuretted hydrogen on the lead. Constipation is a marked feature, and there may be painful colic. Peripheral neuritis affecting particularly the musculospiral and peroneal nerves may lead to drop-wrist and drop-foot. There may be depression, delirium, convulsions, and mental changes, with degenerative changes in the cerebral cortex like those of general paralysis.

*Lead poisoning in children*, a fairly common but usually unrecognized disease, presents many points of special interest. It is often mistaken for poliomyelitis. The incidence is highest in infants and young children with erupting teeth, who put painted objects containing lead (yellow paint is specially dangerous) into their mouths. Many suffer from perversion of appetite (pica), and lick the paint off their cribs and the furniture. The child may drink water containing lead or inhale fumes from storage battery casings used in the stove for fuel. In Japan congenital plumbism is common, owing to the pregnant mother covering her face and neck with cosmetics containing lead. Gastro-intestinal symptoms (vomiting, colic, constipation) and anemia may be marked, but the most striking symptoms are those of lead encephalitis, *i. e.*, a change in the mental state, visual disturbances, convulsions and coma. The blood-pressure may be raised, there may be choked disc, and even separation of the cranial sutures. The actual cerebral lesions are merely minute hemorrhages and cellular infiltrations; the symptoms are caused by rapid increase of the intracranial pressure due to intense cerebral edema, as a result of which the brain is swollen, the convolutions flattened, and the medulla pressed into the foramen magnum. The cerebrospinal fluid pressure may be as high as 700 mm. of water (normal 120 mm.). Peripheral neuritis is rare. The lead line on the gums is seldom seen in children (no doubt owing to the healthy condition of the mouth) and stippling of the red cells may be absent. One of the most useful signs is a lead line in the bones in the roentgen-ray film; there are zones of increased density at the growing ends of the long bones, where lead is deposited in place of calcium. This line is rarely absent, even in mild cases.

Much of the lead is stored in the bones. Parathyroid extract, with its well-known effect on calcium metabolism, causes both calcium and lead to be mobilized, removed from the bones, and excreted in the urine. There is a corresponding rise in the blood calcium. Much of the lead can be rapidly removed in this way, but the remainder is firmly united to the bone and is only excreted slowly. Acid-fast intranuclear inclusions may be found in the liver and kidney at autopsy. These inclusions may be of diagnostic value in difficult cases.

**Prussic Acid.** Hydrocyanic acid and the cyanides are suitable for suicidal purposes because they are so rapidly fatal. The poison is not corrosive, but the gastric mucosa has a bright chestnut-brown color. The blood remains fluid. The poison kills by acting on the nervous system and the heart, and there are no special post-mortem lesions, but the characteristic peach-kernel smell can often be detected when the stomach is opened.

**ALKALOIDS.** The poisonous alkaloids such as opium (morphine), strychnine, cocaine, atropine, etc., produce no characteristic postmortem changes. Their detection therefore depends on chemical analysis.

**ALCOHOL. METHYL ALCOHOL.** Methyl alcohol, so common an ingredient in bootleg liquor, and used for "denaturing" ethyl alcohol, is highly toxic. The deaths which follow the drinking of "canned heat," etc., are due to methyl alcohol poisoning. In these cases there is nothing to be found at autopsy apart from severe gastritis and a smell of alcohol in the stomach, lungs, and brain. After a few hours this smell may disappear. If the patient recovers he may be blind from optic atrophy.

**ETHYL ALCOHOL.** Ethyl alcohol may also produce death in a few hours if taken in sufficient quantity and concentration. The postmortem findings are the same as those of acute methyl alcohol poisoning. If the patient has lived a few days there may be marked edema of the brain. The effects of *chronic alcoholism* are very debatable. Undoubtedly resistance to infection is lowered, so that the patient may die of pneumonia, etc. Many degenerative lesions are attributed to chronic alcoholism. Among these are cirrhosis of the liver, chronic gastritis, chronic nephritis, and arteriosclerosis. The direct relation of any of these to alcohol is more than doubtful but it may act as a contributory cause. Chronic alcoholics undoubtedly show a marked fatty degeneration of the liver, a lesser degree of fatty change in the heart and kidneys, atrophy of the seminiferous tubules in the testicle, and cerebral edema or "wet brain."

**CHLOROFORM.** A person may die while under chloroform anesthesia, or may die an acute death after swallowing the liquid. In these cases there are no characteristic postmortem changes apart from the odor of chloroform. The patient may die later of "delayed chloroform poisoning," and autopsy will reveal profound fatty degeneration of the liver, heart, and kidneys. Death is due to interference with the function of these organs, particularly the liver.

**CARBON MONOXIDE.** In carbon monoxide poisoning the gas may come from illuminating gas, from stoves or furnaces, from the products of explosions in coal mines, but the most important source at the present day is the exhaust from automobiles. A car running in a small closed garage will generate enough gas in a few minutes to kill a person. Garage workers breathing a smaller concentration may suffer from a train of symptoms such as headache, vertigo, and weakness. Traffic policemen directing very heavy automobile traffic in large cities may suffer from minor forms of poisoning.

The carbon monoxide combines with the hemoglobin, replacing the oxygen and forming carboxyhemoglobin. The patient therefore dies of asphyxia. But in addition there seems to be a direct poisonous action on the vital centers, for the patient may become unconscious with extraordinary suddenness. It is this rapidity of action which constitutes the great danger of the gas in concentrated form. As the carboxyhemoglobin is of a bright color, the face, the blood, and the viscera assume a cherry-red. This and a markedly fluid blood constitute the chief post-mortem changes. If the patient should live for some days a remarkable bilateral necrosis is found in the lenticular nucleus of the brain, being most marked in or confined to the globus pallidus. It is the iron of the hemoglobin with which the carbon monoxide unites. It is therefore possible that the gas may combine with the iron in the walls of the vessels of the globus pallidus, the iron content being

higher than in any other vessels of the body. The necrosis is probably due to ischemia, which in turn is probably caused by thrombosis of these small vessels.

**BOTULISM.**—Although botulism is caused by a bacterial poison it may for convenience be considered here. The toxin is formed by the *Bacillus botulinus* (*botulus*, a sausage) which grows in spoiled sausages, preserved meat, canned vegetables, fruit, ripe olives, etc., especially those preserved by home canning in which the temperature employed is insufficient to insure sterilization. Thus the poison is ingested ready-made, and is not manufactured inside the body. It is easily destroyed by heat, so that cooking renders the food harmless. It is extremely powerful, and even small amounts may cause death. Like the tetanus toxin it does not act at the point of absorption, for there is never any evidence of gastro-intestinal irritation. The symptoms are entirely cerebral, and are apt to be mistaken for those of epidemic encephalitis. Indeed, the first cases of the latter disease which appeared in England were thought to be examples of botulism. The most characteristic symptoms are ophthalmoplegias (squint, double vision), ptosis, and difficulty in swallowing and in speech. All of these are due to cranial nerve palsies. The postmortem findings are merely those of toxemia—cloudy swelling, petechial hemorrhages, etc.

## ADDITIONAL READING

**Carbon Monoxide Poisoning.** MARTLAND: J. A. M. A., 1934, 103, 643.

**Industrial Poisons.** HAMILTON: Industrial Poisons in the United States, New York, 1925.

**Lead Poisoning.** AUB, *et al.*: Medicine, 1925, 4, 1. MCKHANN AND VOGT: J. A. M. A., 1933, 101, 1131.

## Chapter

## 14

# HEREDITY AND CONSTITUTION IN DISEASE

### HEREDITY IN DISEASE

IN the causation of disease two great factors always demand consideration; these are environment and heredity. So far we have been concerned for the most part with the environmental diseases, those caused by bacterial, animal parasites, trauma, physical irritants, chemical poisons, etc. For the last century or more, medicine has concerned itself with these extrinsic agencies which are more readily studied and for which more can be done than in the case of hereditary defects of the germ plasm. Far reaching and profound observations have been made in the past, above all by the Austrian monk Gregor Mendel in 1866, but the modern study of heredity and the explanation of the phenomena observed by Mendel date from the beginning of the present century with the rediscovery of his principle of segregation in 1900. This study has served to show, were the proof needed, that men are not created free and equal, but handicapped from the beginning.

**THE INHERITANCE OF DISEASE.** Unit characters may be transmitted from parents to offspring, and their characters, depending on whether they are dominant or recessive, will appear in the first or second generation *provided the breeding is controlled*. In addition to such characters as color, shape, size, fertility, vigor, length of life, etc., definite defects may also be transmitted, and these constitute hereditary disease in man. It is at once evident that the study of these defects is a very different matter from the investigation of the mode of transmission in peas and guinea-pigs, for in the case of man breeding is a matter of chance beyond control. Many of the hereditary diseases are relatively rare. For these reasons there has been a tendency on the part of the medical profession to minimize the importance of heredity and to exalt that of environment. There is a growing feeling, however, that many of the commoner degenerative conditions of middle life, such as arteriosclerosis, may have their genetic representation in the germ plasm.

A distinction is sometimes drawn between *familial* and *hereditary* disease. This distinction is entirely imaginary, for familial diseases are always hereditary. When both parents must transmit the defect before it becomes recognizable we have the so-called familial cases, but this is merely an example of a recessive character. The parents need not and generally do not exhibit the defect themselves, as is evident to anyone familiar with the principles of genetics. A "familial disease" is one in which the pathological character is recessive, a "hereditary disease" is one in which it is dominant. A recessive character may be transmitted indefinitely in the germ plasm without coming to light until it meets a similar recessive from another strain. Disease factors in man are generally dominant, but they may be recessive or sex-linked. A disease, *e. g.*, diabetes mellitus, may in one family appear to be hereditary and in another familial, depending on the distribution of the genes for diabetes in the chromosomes. A *congenital* defect is one which is present at birth, although it may only develop later to a sufficient degree to be detected clinically, *e. g.*, congenital cystic kidney, congenital cerebral aneurism. This defect may be hereditary, but

frequently it is acquired *in utero*; congenital syphilis, for instance, should not be called hereditary syphilis, for it is not transmitted by the germ plasm.

*Simple Dominant Inheritance.*—This is the simplest type to recognize. Each affected individual has an affected parent and grandparent. The heredity is not sex-linked. Examples are brachydactyly (short fingers and toes), multiple cartilaginous exostoses, progressive pseudohypertrophic polyneuritis, Huntington's chorea, multiple polyposis of colon and rectum, sickle-cell anemia, diabetes insipidus and angioneurotic edema. All of these diseases are commoner in the male, and are often transmitted by the male. In one family there were 23 cases of diabetes insipidus among 91 members in 4 generations.

*Simple Recessive Inheritance.*—It is much more difficult to recognize a simple recessive heredity from the family history than a simple dominant. The factor must be present in a duplex condition from both parents in order that the individual may show it. The affected individual results from the mating of two parents who are outwardly normal, but are really heterozygotes or hybrid carriers ( $DR + DR = DD$ , 2  $DR$  and  $RR$ ,  $RR$  being the only one to exhibit the disease). Normality is nearly always dominant to defectiveness. That is one of the blessings of a recessive character. A lethal gene may be paired with a normal (dominant) gene, but its possessor goes through life unconscious of the fact that genetically he is half dead. The factor for the defect may be handed down through many generations of normals, until a chance mating of two heterozygotes occurs. It is inbreeding which is likely to bring out a recessive character. It is of importance, however, to realize that inbreeding (consanguineous marriages as between cousins) is only bad when hidden harmful characters exist in the stock. It is harmless and even beneficial when the hereditary constitution of the stock is sound. Examples in man: amaurotic family idiocy, retinitis pigmentosa, Friedreich's ataxia, alkaptonuria, xeroderma pigmentosum.

*Sex-linked Inheritance.*—Theoretically the character carried by the sex or X chromosome may be dominant or recessive. In practice no examples of dominant inheritance are known. Recessive sex-linked inheritance is very readily recognized, in distinction to the simple recessive autosomal form. The male, who has only one (affected) X chromosome, will exhibit the defect. The female has also one affected X chromosome, but it is held recessive by the other normal X chromosome. She is therefore a heterozygote or carrier. If by rare chance she should inherit two affected X chromosomes, one from each parent, she would probably show the defect. The carrier female transmits the defect to half her sons, and half her daughters will be carriers (heterozygotes). If both parents are affected, all the offspring will be. The reason why, as a rule, only half the sons inherit the disease and half the daughters become carriers is that in the heterozygous female only one X chromosome carries the taint, and there is an even chance that this is the one which may be lost during maturation of the ovum. The criss-cross inheritance of the sex-linked diseases, the defect traveling by the route father → daughter → grandson is due entirely to the movement of the sex-determining chromosome. Important examples of sex-linked inheritance are hemophilia, color-blindness, night-blindness, and Leber's hereditary optic atrophy.

A very large number of diseases, for the most part rare, are now supposed to have their origin in some hereditary defect in the germ plasm, although, for reasons already discussed, the physician may find it impossible to establish the hereditary factor in an isolated case. A good idea of the number of these diseases can be obtained by consulting the list in Macklin's article in *Medicine*, 1935, 14, 1, or in Crew's *Organic Inheritance in Man*. A few of these merit brief reference.

*Blood diseases* include hemophilia, pernicious anemia and sickle-cell anemia. Hemophilia, a perfect example of a sex-linked recessive character, has already been considered. Pernicious anemia usually gives little or no evidence of a hereditary

tendency unless a very full family tree can be drawn up, but several cases of achylia gastrica may be found in the same family, and this condition undoubtedly precedes the onset of pernicious anemia. It looks as if the achylia were a hereditary character, the operation of some extraneous factor occasionally precipitating in such persons an attack of the disease. Sickle-cell anemia behaves as a dominant. Eosinophilia may be familial. I have studied two brothers, in one of whom the eosinophils averaged 80 per cent and in the other around 20 per cent. Hemorrhagic telangiectasis, a condition characterized by spontaneous bleeding from dilated vessels in the nose and mouth and the appearance of red spots in the skin commencing about the time of puberty, behaves as a dominant. One of the most striking examples of human heredity is afforded by the blood groups, the agglutinogens acting as dominants.

*Metabolic disorders* belonging to the group called by Garrod the inborn errors of metabolism are hereditary in origin. Members of this group are alkaptonuria and cystinuria. Diabetes insipidus is a dominant character, at least one parent also showing the defect. The lipid storage diseases (Gaucher's disease, Niemann-Pick's disease, etc.), and abnormal glycogen accumulation (von Gierke's disease) likewise have a genetic basis. Heredity is usually strongly marked in gout.

The *skeleton* is often the site of hereditary defects. Multiple cartilaginous exostosis is also known as hereditary deforming chondrodysplasia, a name which announces the inherited nature of the defect. Brachydactyly, or short fingers, the first example of Mendelian inheritance demonstrated in man, is a simple dominant. The fingers have only two phalanges, the second and third being fused owing to absence of an epiphysis in the former. A similar type of defect in the hand has been transmitted from one of Henry the Sixth's nobles in the 15th century to descendants living at the present day; the recently exhumed skeleton of the original earl showed the same bony change. Fragilitas ossium, a condition characterized by multiple fractures and sometimes associated with blue sclerotics, may show a very marked familial tendency, nearly always dominant. Males and females are about equally affected, transmission taking place equally through both sexes.

The *nervous and neuro-muscular systems* furnish a large variety of hereditary diseases. Progressive muscular atrophy, pseudohypertrophic muscular dystrophy (dominant or recessive or sex-linked), Friedreich's ataxia (dominant or recessive), hepatolenticular degeneration (Wilson's disease), peroneal atrophy, amyotonia congenita, myotonia congenita and many others are familial in character due to inherited defects in the germ plasma. Muscular tremor may be markedly hereditary, and is usually dominant.

The *skin* and its appendages show a variety of inherited defects. Mention may be made here of baldness, which is markedly hereditary in character. It is much commoner in men than in women, being dominant in males, but recessive in females. The male may inherit it from father or mother, but the mother, being heterozygous, is not bald. Xeroderma pigmentosum, a disease of the skin occurring in childhood and characterized by the occurrence of inflammation when exposed to the sun with subsequent development of multiple cutaneous carcinomata, is recessive in all cases. Von Recklinghausen's disease, or multiple neurofibromatosis, is always dominant, but in some cases pigmented areas take the place of tumors, so that the dominant character is apt to be overlooked.

*Eye diseases* constitute one of the largest groups and serve to fill the blind asylums. Chief among these may be mentioned retinitis pigmentosa and hereditary optic atrophy (Leber's disease), the latter offering an excellent example of a sex-linked disease, being confined to the male but transmitted through the female. Blue sclerotics is an ocular manifestation of a defect of connective tissues in general, including the bones (fragilitas ossium). The blue color is due to the underlying choroid shining through the thin sclerotic. The condition is a good example of a



non-sex-linked defect. It is not transmitted by those not affected, it appears in both males and females, it is transmitted from fathers to sons and daughters and from mothers to sons and daughters. The defect is of course not carried in the sex chromosome. Color-blindness and some forms of night-blindness (the patient becoming blind at dusk owing to lack of the visual purple in the rods of the retina) are both sex-linked. Coloboma of the iris and its extreme form, known as aniridia or absence of the iris causing blindness, are markedly hereditary. Risley records an extraordinary and tragic family history in which one blind man had 13 children who were all blind, 61 blind grandchildren out of 63 and 39 great grandchildren out of 42, a total of 113 blind offspring out of 118. A strong argument for eugenics. Glioma of the retina (retinoblastoma), a neoplasm which is fatal unless removed early, often shows a marked hereditary tendency. In a family of 16, 10 died of this tumor. It is always recessive. There is a marked hereditary tendency in all varieties of cataract, and in amaurotic family idiocy. Strabismus is dominant in some families, recessive in others.

*Mental diseases* are often due to a defect in the germ plasm. Dementia præcox offers a good example. Huntington's chorea is an example of a simple dominant autosomal character. One family from Long Island has furnished practically 1000 cases of this disease. Some types of feeble-mindedness are inherited as simple recessives. Matings of feeble-minded persons with each other gave only 6 normal children out of 482 from 144 such unions (Goddard). The 6 normals may have been a mistake, as in the case of two feeble-minded white parents who had 10 feeble-minded and 2 normal children, but the two normals were black! Amaurotic family idiocy and Mongolian idiocy are always recessive.

*Heredity in cancer* is a difficult matter to pass judgment on. It has already been discussed in connection with tumors, so it will only be touched on here. "In the question of human cancer heredity, all existing statistical evidence is valueless for any exact information on the subject" (Wells). People do not know what their grandparents and great aunts died of, and if they did, the diagnosis would be as often wrong as right. Moreover, an hereditary character may be transmitted through a son incapable of showing that character, *e. g.*, a bull is valuable because it comes of a famous milk-producing strain. A woman with cancer of the uterus may transmit that gene to her son, but it cannot manifest itself; it may be transmitted in the same way to a grandson, and the fatal character may finally appear in his daughter. In such a case it is natural that the heredity tendency should be completely lost sight of. One of the neoplasms in which the influence of heredity is best seen is polyposis of the rectum and colon with its marked tendency to become malignant. Dukes records the case of a man who died of rectal cancer at the age of forty-two years. He had 9 children, 7 of whom developed rectal cancer; 5 were already dead, 1 at the age of twenty-seven years. The disease also appeared in the next generation. It is impossible to believe that in such a case as this there was not some hereditary defect in the germ plasm which acted as a determiner for cancer of the rectum. A man and his wife had cancer of the stomach, and 6 of their 7 children died of the disease. The seventh was killed at the age of twenty-eight years in an accident. In the experimental work on mice the incidence of cancer, its site and its character were all influenced by heredity. It is worthy of note that the larval stage of *Drosophila* suffers from a sex-linked entodermal tumor, which kills one-quarter of the males and is transmitted by the unaffected females.

*Twins* provide a singular opportunity to study the effect of heredity and constitution on disease. In the case of identical (monozygotic) twins, one serves as a control animal for the other. It is as if we were watching one individual leading two physical existences. Margolis and Eisenstein give the following examples, of disease developing more or less simultaneously in both twins: (1) Tumors. Twins developed retinoblastoma of the left eye within a few months of each other. Cancer of the

right testicle appeared in both at the same time. (2) Nervous and mental disease. Dementia praecox, paranoia, and other mental disorders have developed at the same time. (3) Non-infectious systemic disease. At the age of sixty twin brothers developed diabetes characterized by the same set of symptoms, and both died within a few months of each other. Twin sisters in New York and San Francisco developed diabetes at the age of fifty-two and died within a short time of each other. Other diseases which have developed simultaneously in twins are lymphatic leukemia, nephritis, asthma, bronchiectasis, cataract, and Hodgkin's disease. (4) Infections. Twin sisters developed tuberculosis of the right kidney within seven months of each other. Many other similar examples could be given illustrating the profound importance which origin from a common germ plasma has on the development of disease.

## CONSTITUTION IN DISEASE

The subject of constitution is bound up with that of heredity. It has become the custom rather to smile at our medical forefathers when they talk in their writings of the weak constitution of the patient, but the central doctrine of Greek medicine was that of temperaments and constitutions, and the conceptions of Hippocrates are worthy of consideration even at the present day. Constitution, according to Draper, whose monograph on the subject should be consulted, is "that aggregate of hereditary characters, influenced more or less by environment, which determines the individual's reaction, successful or unsuccessful, to the stress of environment." John Hunter, Addison, and other great clinical observers of that period believed firmly that the *habitus* or physical form of the individual bears an important relationship to disease. This physical form is the anatomical aspect of constitution, and although by no means the only aspect it is the one which has been most carefully studied and the only one which will be considered here. "The anatomic features of an individual form one of a set of basic unit characters, predetermined by heredity, and influenced to some extent by environment, which together make up the constitution" (Draper). The anatomical aspect is related to the physiological, psychological and immunological aspects, and it was a recognition of this fact which formed the basis of the marvellous unconscious skill of the older physicians. The three basic elements of the disease problem are Man, the lesion, and the environmental stress, and we are so much engaged with the two latter that the first is apt to be forgotten.

The capacity of an individual to react to the environmental stress is a constitutional quality, just as specific as body size and capable of being transmitted to his offspring. Longevity, which is the result and expression of a good constitution, is certainly inherited; everyone knows of families, the majority of whose members reach the late seventies or eighties, no matter what kind of life they may have led. We have already seen that this is the case with resistance to infection. Sex, which is considered below, has a profound influence on disease reactions, and this is determined by the presence or absence of an extra chromosome. In some way this must be linked with the commonness of gall-bladder disease and the comparative rarity of chronic peptic ulcer in the female. Size of body has been shown in animals to be a unit character. The entire skeleton may be altered by a defect in a single gene, and the person may be a giant or a dwarf. In this instance the determiner appears to act through an endocrine gland (pituitary). Race may play a part in predisposition to a disease. Thus certain diseases are peculiar to the Hebrew race. Amaurotic family idiocy is practically confined to Jewish children, while Gaucher's disease and Niemann-Pick's disease are much commoner in these children; Buerger's disease, diabetes mellitus, and pentosuria are commoner among Jews.

The *habitus* or general build of the body is a resultant of a combination of height and weight. On this basis it is possible to divide persons into the sthenic and as-

thenic groups. The *sthenic* individual is short and stout, with a wide costal angle and deep chest, inclined to be florid, of cheerful sanguine disposition, liable to gall-bladder disease, arterial hypertension and likely to die of arteriosclerosis, apoplexy or coronary occlusion owing to defects in his germ plasm at the time of conception. The *asthenic* individual is tall and thin, with a narrow costal angle, a pallid countenance, easily fatigued and inclined to be melancholy; he has a long, drooping stomach which empties poorly and intestines which sag, so that his melancholy may be aggravated by dyspepsia and constipation. He is a likely subject for peptic ulcer. He seldom has heart or arterial disease and is likely to be long-lived if he escapes tuberculosis in youth. The gall-stone man seldom has ulcer; the ulcer man seldom has gall stones. The pages of Shakespeare and Dickens are filled with immortal characterizations of these types.

**THE INFLUENCE OF SEX.**—The question of sex has already been considered in connection with sex determination and the sex-linked inheritance of disease. We have now to consider sex from the standpoint of human constitution, *i. e.*, the manner in which it influences the reaction of the individual to the stress of environment. In such a discussion the organs peculiar to either sex must be excluded, only those common to both being considered. When this is done the surprising fact emerges that very few serious organic diseases are commoner in the female. Most diseases of the gastro-intestinal tract, respiratory tract, blood vessels, heart, bones, joints and urinary tract are commoner in males than in females. Some diseases such as thromboangiitis obliterans are almost confined to the male, while others such as angina pectoris, coronary occlusion, peripheral arteriosclerosis, pernicious anemia, leukemia, lymphosarcoma, etc., are more frequent in that sex. The gall-bladder is a notable exception to the general rule, and to a lesser degree mitral stenosis. Functional disorders, on the other hand, such as Raynaud's disease, hypertension, migraine, hysteria and chronic nervous exhaustion are commoner in the female. There is a higher mortality for the male throughout all the periods of life. This cannot be explained away, as is commonly done, by reference to overwork, industrial hazards, abuse of alcohol and tobacco, venery, etc., for the difference in the sex mortality is most striking in intrauterine life and during the first few years of childhood. There appears to be an inherent weakness in the male, a sex-linked inferiority, so that by comparison with the female he is a weakling at all periods of life from conception to death. This holds true throughout the animal kingdom, the males being shorter-lived. As Allen remarks, the price of maleness is weakness, and woman is far from being "the weaker vessel." Only a few organic diseases, such as those of the gall-bladder and thyroid, are commoner in females.

#### ADDITIONAL READING

**Constitution.** DRAPER: Human Constitution, Philadelphia, 1924.

**Sex and Disease.** ALLEN: Ann. Int. Med., 1934, 7, 1000.

**Tumors.** MACKLIN: Am. J. Surg., 1933, 21, 438. PACK AND LEFEVRE: J. Cancer Res., 1930, 14, 167. WARTHIN: J. Cancer Res., 1928, 12, 249. WELLS: J. A. M. A., 1923, 81, 1021, 1103.

**Twins and Disease.** MARGOLIS AND EISENSTEIN: Ann. Int. Med., 1933, 6, 1489.

## PART II.—SPECIAL PATHOLOGY

### Chapter

### 15

### THE HEART

**DESCRIPTIVE OUTLINE.**—In describing the gross appearance of the heart one must consider the pericardium, pericardial cavity, the size and weight of the heart, the myocardium, auricles, ventricles, endocardium, valves (cusps), valvular openings and coronary arteries. The *pericardium* is smooth, shiny, thin and translucent. There is a varying amount of subpericardial fat. The *pericardial cavity* contains from  $\frac{1}{2}$  to 1 ounce (10 to 30 cc.) of clear, straw-colored, serous fluid. The *size* can only be learned by frequent observation of the normal. It may be increased or diminished in disease. The average *weight* is 300 grams in the male, 250 grams in the female, but these figures will be considerably exceeded in a big muscular laborer or reduced in a tiny fragile woman. The weight is largely dependent on the thickness of the left ventricle, and varies directly with the arterial blood-pressure, of which it is a fairly reliable indication. The *myocardium* has the reddish-brown color of voluntary muscle, and a consistence which may be increased or diminished in disease. To *open the heart* begin with the right auricle, passing the scissors through the mouths of the superior and inferior vena cava, and follow the direction of the blood flow into the right ventricle, left auricle, left ventricle, and aorta. The *cavities* of the auricles and ventricles are noted for dilatation and their walls for hypertrophy. The *wall of the right ventricle* is about 5 mm. thick, that of the *left ventricle* 10 to 15 mm. The *endocardium* lining the cavities is smooth, shiny and translucent so that the underlying muscle can be seen, but frequently the lining of the left auricle is thickened, white and opaque. The *valve cusps* should be as thin and smooth as fine silk. The commissures of the aortic valve, *i. e.*, the points where the cusps are joined together, have no appreciable thickness; any widening of these commissures is an indication of disease. As regards the *valvular openings*, the mitral should admit two fingers (two cusps) and measure about 7.5 cm. in circumference; the tricuspid should admit three fingers (three cusps) and measure about 10 cm. in circumference. The *chordæ tendineæ* attached to the mitral valve are slender fibers which may become thickened and shortened. Finally, the *coronary arteries* are opened and inspected.

The heart consists of three main anatomical elements, the myocardium, the pericardium and the valves. Any or all of these may be the seat of organic disease. It must be remembered, however, that no organ is influenced to so marked a degree by nervous stimuli and what are commonly referred to as the emotions. As my colleague, Dr. Allan Walters, has pointed out, the simple everyday words of our language testify to the truth of this statement. We say that a person is heavy-hearted, hard-hearted, heartless, good-hearted, that his heart aches with loneliness,

flutters with alarm or stops with fear. Although cardiac symptoms may, therefore, have an emotional rather than an organic basis, we are concerned in this place primarily with structural changes.

## LESIONS OF THE VALVES

**Rheumatic Disease of the Heart.** The heart is a pump, and as impairment of the valves of a pump will wreck its efficiency it is natural that attention should have been focussed on rheumatic disease of the valves (endocarditis). Rheumatism, however, is a pancarditis, an infection of the fibrous tissue of all parts of the heart (endocardium, myocardium, and pericardium), nor does the aorta escape.

The bacteriology and the general pathology of rheumatic fever have already been discussed in Chapter 7. It was there pointed out that the disease was an infection of the fibrous tissues of the body accompanied by the formation of a characteristic pathological lesion, the Aschoff nodule. This lesion is seen in most typical forms in the myocardium, but lesions sufficiently distinctive to be recognized occur in the cardiac valves, pericardium, synovial membrane, periarticular tissues, skin, etc. The damage is primarily to the supporting tissues, *i. e.*, collagen and elastic tissue. The first change is fibrinoid degeneration, followed later by actual necrosis. Exudation characterizes the early stages, proliferation the later and finally fibrosis. In the valves this leads to postinflammatory adhesions and contraction with accompanying stenosis or incompetence, in the myocardium it leads to scarring, and in the pericardium to adhesions. Rheumatism may lick the joints, especially in children, but it certainly bites the whole heart. It is the valvular rather than the myocardial damage which is the chief threat to the patient. Rheumatic heart disease is predominantly a disease of childhood, youth and early adult life. Probably more than 70 per cent of the cases occur before the age of twenty, the peak of onset being between the ages of five and ten.

There seems to be no doubt that allergy plays an important part in the production of acute rheumatic lesions, although the evidence is only indirect and circumstantial. Periarthritis nodosa has been reproduced by Rich and Gregory experimentally by injecting serum into previously sensitized animals. Cardiac lesions similar to those of rheumatic fever were present in these animals. McKeown, injecting horse serum into rabbits previously sensitized, produced lesions confined to the cardiovascular system. The lesions were identical with those of human rheumatic fever, and were present in the myocardium, endocardium and valves. In some animals the only lesion was valvulitis. The serum lesions were found most frequently in the mitral valve, and were never seen in the pulmonary valve. It is believed that the factor responsible for sensitization in acute rheumatism is the hemolytic streptococcus.

**VALVULAR LESIONS.**—By far the commonest valvular defect resulting from rheumatic fever is mitral stenosis. In the aortic valve there may be a moderate degree of incompetence (never so complete as in the syphilitic form) or, more rarely, stenosis which years later may take the form of so-called calcific sclerosis. The lesions of the valves on the left side are more extreme owing to the greater strain on those valves. The mitral valve suffers more frequently in women, the aortic valve in men. The reason for this is not known. If the valve ring, to which the cusps are

attached and which is really the proximal part of the valve, be examined microscopically, all four valves will be found to be involved in most cases (Gross and Friedberg). In the mitral and aortic valves the process is usually progressive, less often in the tricuspid, and least in the pulmonary, so that in the two latter gross lesions are correspondingly rare. Infection seems to begin in the valve rings, although the primary focus in the case of the mitral is probably the wall of the auricle, and in the case of the aortic the root of the aorta. Infection may readily spread between the mitral, aortic and tricuspid rings by way of the intervalvular fibrosa and the septum



FIG. 163.—Rheumatic endocarditis. A bead-like row of vegetations runs along the line of contact of a cusp of the mitral valve.

fibrosum. The close proximity of a fibrous pericardial wedge to most of the valve rings favors spread of infection from pericardium to valves. It must be understood that the rings may show microscopic lesions although the cusps remain free.

The essential lesion in rheumatic endocarditis is the presence of rheumatic nodules in the endocardium of the valves. This leads to a diffuse thickening of the cusps. An additional although not essential feature is the formation of rheumatic vegetations. These are tiny bead-like warty (verruccose) nodules arranged in a row along the margin of contact (not the free margin) of the cusps, and therefore on their proximal aspect. (Fig. 163.) They consist of platelet thrombi deposited on the raw surface which results from trauma to the endothelium of the valve along the line of contact. This trauma is greatest on the left side of the heart where pressure is highest, but when mitral incompetence develops the pressure on the right side also rises, so that if the infection recurs vegetations will be formed on the tricuspid valve. They are firm and adherent, so that they are not detached by the heart's action. For this reason embolic phenomena are not seen in rheumatic endocarditis. When they are rubbed off, the underlying surface is raw. The mural endocardium may also be involved. On the posterior wall of the left auricle just above the mitral valve there may

be a rough thickened patch which becomes scarred later, and may form a nidus for *Streptococcus viridans*. This is often called the *MacCallum patch*.

The microscopic picture is that of a valvulitis as well as an endocarditis. Many new vessels have been formed in the thickened valve, and inflammatory cells are grouped in relation to these vessels. These are the same cells which constitute the Aschoff nodule, of which the most characteristic is the large multinucleated Aschoff cell, but the arrangement is more diffuse and less distinctive than it is in the myocardium. Leary has described a special type of endocardial lesion in the very early cases. This takes the form of a palisade of cells set at right angles to the surface along the contact edge of the valve. Edema, a marked feature of the inflammatory lesion, accounts for much of the swelling of the valve. There is fibroblastic proliferation, followed later by the production of fibrous tissue. Meanwhile the endothelium covering the cusps degenerates, particularly along the line of closure, and is soon lost. Platelets are deposited on the raw surface together with a certain amount of fibrin, and it is these which form the vegetations. Fibroblasts and capillaries invade the vegetations, and these become converted into granulation tissue and organized, so that finally they blend with the thickened valve and become indistinguishable. The inflammation is not confined to the valves, for the endocardial lining of the left auricle may show the same type of lesion. In the acute stage there is roughening and in the chronic stage thickening of the surface lining. The chordæ tendineæ may contain Aschoff nodules, and the subsequent fibrosis causes shortening of these cords which is so marked a feature of mitral stenosis. In old lesions of the mitral valve the cusps show gross vascularity, the principal vessels being small thick-walled arteries or arterioles of musculo-elastic type (Koletsky). This vascularity may be regarded as one of the stigmata of rheumatic fever.

The consequences of all this are fatal to the health and efficiency of the valve. During the acute stage the inflamed edges of the cusps adhere together, and with the onset of fibrosis these adhesions become very firm, so that the cusps cannot open as they should, and there is narrowing or stenosis of the valves, both mitral and aortic. The new fibrous tissue makes the cusps rigid, and its contraction both in the cusps and in the chordæ tendineæ still further aggravates the stenosis so that the mitral opening may appear as a mere slit or button hole, or as a rigid funnel when viewed from the auricular aspect. Calcification of the injured cusps is common. It attains its most extreme form in the aortic valve of men over middle age in the lesion known as calcified nodular aortic stenosis.

**MYOCARDIAL LESIONS.** The typical myocardial lesion is the Aschoff nodule, which is fully described in Chapter 7. There is little to be seen in the gross appearance of the muscle in an acute case except a dilatation of the left ventricle, but tiny white specks may be seen under the endocardium of the left ventricle and left auricle. These are the Aschoff bodies. They are scattered through the fibrous tissue of the myocardium, most abundant at the base of the interventricular septum, numerous in the left auricle, not so common on the right side. They are submiliary in size, oval or lemon-shaped, and consist of a central necrotic, reticulated area, lymphocytes, plasma cells, and the characteristic large multinucleated Aschoff

cells. (Fig. 164). They are usually found in the adventitial coat of medium-sized arteries. The so-called Anitschkow myocyte is often found in large numbers in the cardiac lesions although not in rheumatic lesions elsewhere. It is a cardiac histiocyte which in inflammation shows increased cytoplasm, a highly characteristic serrated bar of chromatin in the center of the nucleus, and fibrils radiating from the bar to the periphery. For a detailed account of the finer features of the Aschoff body the paper by Gross and Ehrlich should be consulted, in which will be found a description of the various stages of the life cycle through which the lesion passes. Fibroblasts are abundant and lay down collagen fibers, which replace the inflammatory lesion when the infection has died down. This may not happen for a long



FIG. 164.—Large multinucleated Aschoff cells.  $\times 1100$

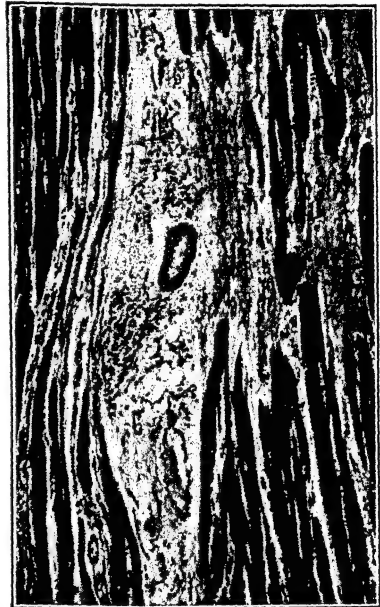


FIG. 165.—Healed Aschoff body.  $\times 50$ .

time, and Aschoff bodies have been found a number of years after the attack of rheumatic fever. As a result of the inflammation there is a varying degree of myocardial destruction, sometimes very great. The end-result is scarring. As the Aschoff lesion usually lies alongside a blood vessel, so the rheumatic scar often is at the side of or surrounds a small artery. (Fig. 165.)

Aschoff nodules may not be found, for they are present in only about 80 per cent of cases. There may be a diffuse type of lesion instead of the circumscribed nodule. This is especially common in the wall of the left auricle, and the damage it causes may be responsible for subsequent auricular fibrillation. Moreover the Aschoff nodule is merely the productive feature of rheumatic pathology. The exudative feature, though less marked



in the myocardium than in the joints, is also important. The inflammatory edema, which is transient, no doubt interferes temporarily with the conduction bundle, and is responsible for the temporary functional disturbances which electrocardiographic studies show to be present in over 90 per cent of cases of rheumatic fever.

**PERICARDIAL LESIONS.** Rheumatism is the commonest cause of acute pericarditis. The acute stage presents little that is characteristic of rheumatism; it is merely an acute serofibrinous inflammation of a serous membrane. The fluid exudate is small in amount, only a few ounces, and is serous, never purulent. The chief element is the fibrin which is deposited on both surfaces of the pericardium giving it a shaggy or "bread-and-butter" appearance, as if two slices of buttered bread had been stuck together and then pulled apart. Even where no fibrin can be seen the natural gloss of the membrane is lost, but this may have to be looked for carefully.

In the *microscopic* picture any rheumatic lesions are apt to be hidden by the acute inflammatory reaction, but an occasional Aschoff body may be found in the subendothelial tissue. The surface endothelium is cast off, successive layers of fibrin are laid down, and this becomes organized by the invasion of new vessels and fibroblasts. The inflammatory cells are mostly lymphocytes and plasma cells with only an occasional polymorphonuclear leucocyte. The inflammation extends through the subpericardial fat down to the heart muscle.

The *after-effects* vary. There may be merely one or two opaque white patches of thickened epicardium known as *milk spots*. If absorption of the exudate is less complete there may be numerous adhesions. Finally there may be a completely *adherent pericardium*. Calcification of the lesions may occur, so that stony plates are formed on the surface of the heart.

**AORTIC LESIONS.** The fibrous tissue of the aorta suffers in common with the fibrous tissue of the heart, so that Aschoff bodies or more diffuse lesions may be found in the adventitia. Although scars of the media have been described it is doubtful if these lesions ever weaken the wall sufficiently to produce an aneurism, thus differing from the similar but more extensive and destructive lesions of syphilis.

**RELATION OF SYMPTOMS TO LESIONS.**—The *endocardial* symptoms or rather signs are the cardiac murmurs. The mitral systolic murmur is due to mitral regurgitation, which in turn is due to myocardial weakness and dilatation of the auriculo-ventricular ring. The mitral diastolic murmur, on the other hand, is valvular in origin, and is due to the stiffness of the cusps and the narrowing of the opening. The intensity of the murmur depends on the power of contraction of the auricle, and as this becomes weaker in the late stages, so the murmur may grow faint. Aortic incompetence with its diastolic murmur is due to retraction of the cusps and not to myocardial weakness, thus differing from mitral incompetence. Aortic stenosis due to rheumatism is uncommon. The symptoms of cardiac failure are due in the main to valvular disease. The *myocardial* effects may be acute or chronic. In the acute stage there may be death due to ventricular failure. In the chronic stage auricular fibrillation develops, owing to the degenerative lesion blocking the path of the impulse so that it goes around in a circle, and the pulse becomes totally irregular. The chief *pericardial* symptom is pain, just as the chief sign is a friction rub. Pain is often absent, though friction may be well marked. The friction rub is due to the rough surfaces rubbing together, but it is probable that some degree of tension and stretching is necessary before pain is produced, as is the case with pleural pain.

**Subacute Bacterial Endocarditis.**—Endocarditis due to demonstrable bacteria may be subacute or acute. Before the introduction of penicillin the subacute form used to run a course of from two months to one or two years, whereas the acute form was fatal in less than six weeks.

**SYMPTOMS.**—The principal clinical features are continued fever, evidence of multiple embolism, endocarditis, a positive blood culture (streptococci), enlargement of the spleen, and clubbing of the fingers. As a cause of continued fever the disease should be classed with tuberculosis, typhoid fever, sepsis, and undulant fever. If a patient with a history of previous rheumatic fever or the physical signs of mitral stenosis or aortic stenosis or incompetence develops persistent evidence of toxemia such as malaise, weakness and fever, subacute bacterial endocarditis may be diagnosed even in the absence of embolic phenomena and a positive blood culture. The embolic phenomena are very varied: there may be crops of petechial hemorrhages in the skin, painful cutaneous nodules (Osler nodes), hemiplegia (cerebral vessels), sudden blindness in one eye (retinal artery), petechial hemorrhages in the retina, each with a white center (Roth's spots), pain in the splenic region, blood in the urine, diarrhea, and vomiting (mesenteric vessels). The blood may show a progressive anemia and a moderate leucocytosis, but often there is leucopenia with relative lymphocytosis.

Formerly the outlook in fully developed cases was practically hopeless. The heart was indeed beating muffled marches to the grave. The advent of penicillin therapy has greatly altered this outlook. When this agent is used sufficiently long and in sufficiently large doses the results are remarkably good. In many cases the blood rapidly becomes bacteria-free and the course of the disease is arrested. Much depends on the sensitivity of the strain of infecting streptococci to penicillin. Even when all the bacteria are finally killed, however, the patient may be left with badly damaged valves, and he may suffer from congestive heart failure and other cardiac complications.

**ETIOLOGY.**—As a rule the infection attacks previously damaged valves. An active or healed rheumatic lesion is present in from 75 per cent (Gross and Fried) to 90 per cent (Clawson) of cases. A congenital bicuspid aortic valve is a predisposing condition. Syphilis of the aortic valve is a rare antecedent. In a minority of cases the valves were previously healthy.

In about 95 per cent of cases the infecting organism is *Streptococcus viridans*, so that the condition is sometimes called streptococcus viridans endocarditis. The organism is of low virulence for animals; the fatal issue seems to be due to the failure of the immunological forces rather than to the virulence of the germ.

The probable *source of infection* is the mouth and throat. Transient bacteriemia, mostly with *S. viridans*, is common after tooth extraction and tonsillectomy, especially when the gums are infected (Okell and Elliott). Even biting on hard candies will cause an immediate blood infection in cases of pyorrhea. It is easy to understand how a valve damaged by rheumatism or by a congenital defect may be attacked by these circulating organisms.

**LESIONS.**—The lesions may be divided into three groups: (1) cardiac, (2) embolic, and (3) general.

1. The *cardiac lesions* are mainly *valvular*; myocardial and pericardial lesions do not play a prominent part as they do in rheumatic disease of the heart. It seems probable that the infection is implanted on the surface

of the injured valve, rather than carried into its substance by newly formed vessels. The mitral valve is most often involved, the aortic valve coming next. Infection of the pulmonary valve is very rare.

The lesions are proliferative rather than destructive, but occasionally large portions of the cusps are destroyed as in the acute ulcerative form. The characteristic lesion takes the form of large friable, polypoid vegetations, very different from the tiny firm vegetations of rheumatic endocarditis. (Fig. 166.) They originate along the line of contact (proximal aspect of the cusp), but may cover the valve. At autopsy part of the valvular lesion may be calcified, showing that there have been attempts at healing. A highly characteristic feature is a tendency for the vegetations to spread on to the mural endocardium. This may be from the mitral



FIG. 166. Subacute bacterial endocarditis. The friable vegetations, the mural spread, and the old thickening of the aortic cusps are all very characteristic.

valve to the wall of the left auricle or the chordæ tendineæ which may be weakened and rupture, or from the aortic valve to the wall of the ventricle. The distribution of the vegetations on the left auricle corresponds with that of the rheumatic lesion (MacCallum patch) in that region.

*Microscopically* the vegetations are amorphous masses consisting of fused platelets and fibrin. (Fig. 167.) A striking feature is the presence of masses of bacteria on the surface of the vegetations. They are best shown by Gram's stain, (Fig. 168) but are quite evident in hematoxylin and eosin preparations. In some cases they are buried beneath a mass of platelets and fibrin; in such cases the blood culture may be negative. The valve itself is infiltrated by mononuclear cells, which are most numerous at the attachment of the vegetation to the cusp. Larger multinucleated cells not unlike Aschoff cells may be present. There is a remarkable absence of polymorphonuclear leucocytes. No bacteria are found in the substance



FIG. 167.—Subacute bacterial endocarditis. Large vegetation on thickened valve with masses of bacteria on the surface.  $\times 6.6$ .



FIG. 168.—Subacute bacterial endocarditis. Bacteria stained black on surface of lesion. In this type of case the blood culture would probably be positive.  $\times 50$ .

of the valve where the cells are, and there are no cells among the bacteria. That is the weakness of the situation from the immunological standpoint. Fibroblasts are present in the deeper parts of the lesion, and calcification is not uncommon. There is thus a distinct tendency to repair.

*Myocardial lesions* are not common. There may be Bracht-Wächter lesions, little collections of polymorphonuclear leucocytes around necrotic material, practically tiny abscesses. In other cases Aschoff bodies may be present. In the *pericardium* petechial hemorrhages are common; but pericarditis is rare.

2. *Embolic lesions* are very common, as the vegetations are friable and easily detached. They are non-suppurative, in contrast to the suppurative embolic lesions of acute ulcerative endocarditis. The petechial hemorrhages in the *skin* and the Osler nodes are usually regarded as embolic in origin, but there is no proof of this. It is more likely that they represent a perivascular reaction to the endotoxin, possibly allergic in nature. Large infarcts due to blocking of medium-sized vessels are seen in the enlarged *spleen* and in the *kidneys*. Many of the more minute lesions appear to be due to toxic necrosis of vessel walls rather than to emboli, although the name embolic is still retained. This is particularly true of the so-called *focal embolic glomerulonephritis* originally described by Löhlein and known as the Löhlein lesion. Only a few glomeruli are involved and usually only a part of a glomerulus. A few loops of the tuft are blocked with an accompanying acute reaction, as a result of which red blood cells appear in the capsular space and pass out into the urine. Although these lesions were commonly believed to be embolic it appears more probable that the blocking of the loops is due to capillary thrombosis and necrosis. Healing occurs owing to the ready access of cells to the irritant, and a homogeneous mass of organized tissue is formed in one segment of the tuft, giving an appearance which is pathognomonic of this disease. In the acute stage small red spots are seen on the surface when the capsule is stripped off, an appearance known as the "flea-bitten kidney." Occasionally there is a diffuse glomerulonephritis with renal insufficiency terminating in uremia. In the *central nervous system* there may be cerebral embolism and softening in the internal capsule with a resulting hemiplegia, or tiny inflammatory lesions may be scattered through the brain. The *retina* may show pathognomonic transient "canoe-shaped" elliptical hemorrhagic spots with a pale center. *Mycotic aneurisms* may be produced in the cerebral, superior mesenteric, and other arteries.

3. The *general lesions* are of less importance. Some are due to cardiac failure, some to toxemia. Among the latter are cloudy swelling and fatty degeneration of the liver and kidneys, enlargement of the spleen, a secondary anemia, and in rare cases degenerative lesions of the spinal cord like those of subacute combined degeneration.

The *relationship to rheumatic heart disease* has been investigated by a number of workers (Clawson and Bell, MacIlwaine). Although bacteria are so abundant in the one disease and lacking in the other, the feeling is that in many cases of subacute bacterial endocarditis the bacterial lesion is superimposed on a heart which is at the time of infection the site of active rheumatic carditis, and that the two diseases are etiologically similar although differing in their tissue response to the infecting agent.

**RELATION OF SYMPTOMS TO LESIONS.**—The *cardiac signs* (murmurs) are due to the vegetations and the valvular destruction. But at first there may be no murmurs, and of course murmurs are no proof of an active endocarditis. Later in the disease the valvular insufficiency leads to cardiac decompensation and enlargement of the heart. Cardiac pain is not uncommon. I know no explanation of this. Death is usually due to cardiac failure, cerebral embolism, uremia, or some intercurrent infection.

The *embolic phenomena* are readily explained by the friable nature of the large soft vegetations. The blood in the urine which is so characteristic a feature is due to the thrombotic glomerular lesions. It is better to speak of red blood cells rather than blood, for the microscope is generally needed for their detection, and as they are not present every day the examination may have to be repeated a number of times. The occasional occurrence of renal insufficiency and uremia is due to a rather uncommon diffuse glomerulonephritis.

**Acute Bacterial Endocarditis.**—This is a group, a good deal less common than the preceding form, in which an acute destructive process is caused by pyogenic cocci which produce suppurative lesions not only in the valves but also in the organs where emboli lodge. The course of the disease used to be six weeks or less, so that this form was called malignant endocarditis, but the use of antibiotics has changed all this. The chief bacteria responsible are *Streptococcus hæmolyticus*, *Staphylococcus aureus*, pneumococcus, and occasionally gonococcus. The primary focus of infection is usually obvious, being some suppurative lesion of the skin (boil, carbuncle), bones (osteomyelitis), uterus (puerperal sepsis), lung, or prostate.

The two chief features of the valvular lesions are the very large, exuberant, friable vegetations and the marked destruction, so that a cusp may be perforated or largely ulcerated away and the chordæ tendineæ destroyed. The mitral and aortic valves are affected with equal frequency, and the tricuspid often suffers. Endocarditis of the tricuspid alone occurs in heroin addicts who develop staphylococcal septicemia from contaminated intravenous injection of the drug. In most cases it is impossible to distinguish between the acute and subacute forms from the gross appearance. The *microscopic* picture is one of acute suppuration, the cusp being crowded with polymorphonuclear leucocytes. The vegetation has the same microscopic appearance as in the subacute form.

*Embolic abscesses* are formed in all parts of the body, especially the skin, myocardium, brain, and kidneys. Both kidneys are riddled with abscesses, a condition known as the pyemic kidney. The general clinical and pathological picture at the time of death is one of acute pyemia.

**THROMBOTIC NON-BACTERIAL ENDOCARDITIS.**—It has long been known that in many chronic diseases (nephritis, diabetes, cancer) small nodules may be found on the valves at autopsy, a condition known as terminal endocarditis. The basic lesion here, and probably in all other forms of endocarditis, is a degeneration and swelling of the valvular collagen with depolymerization of the mucopolysaccharides of the ground substance and a tendency to necrosis. This is a degenerative endocardiosis rather than a true endocarditis (Allen and Sirota). The reactivity of the collagen is probably controlled by such factors as endocrine function, reaction to stress, and the state of nutrition. If the destructive process is more severe, platelets are deposited on the damaged valve and true thrombotic verrucae are formed. This is the condition called thrombotic non-bacterial endocarditis (Gross and Fried-

berg). If infection supervenes, subacute or acute bacterial endocarditis will result, depending on the type of infecting organism. It seems probable that all forms of bacterial endocarditis develop in this manner.

The incidence of the different forms of endocarditis encountered at autopsy has changed remarkably since the advent of chemotherapy and antibiotics (Angrist and Marquiss). There has been a marked decrease in bacterial endocarditis and a corresponding increase in the non-bacterial forms of the disease. Transitional forms between the non-bacterial and bacterial types and between the acute and subacute varieties are now seen much more frequently, as are healing phases of the latter forms.



FIG. 169. —Mitral stenosis. Small left ventricle, narrowing of mitral opening, great dilation of left auricle and right side of heart.

### CHRONIC VALVULAR DISEASE

**Mitral Stenosis.** — Most, if not all, cases of mitral stenosis are rheumatic in origin. It is possible that mild forms of subacute bacterial endocarditis may end in healing with adhesion of the cusps. It is much commoner in women than in men. The left auricle and the right side of the heart are greatly dilated owing to the obstruction, but the left ventricle is normal in size or even smaller than normal. (Fig. 169.) When the heart is opened the left auricle is seen to be enormous. It may contain as much as 500 cc. instead of the ordinary 30 or 40 cc. The valve looks like a deep funnel, the walls of which are formed by the fused cusps. The blood rushing

through this rigid funnel causes a vibration of its walls which is responsible for the diastolic murmur and thrill with or without presystolic accentuation. The opening may be a mere button-hole which will hardly admit the tip of the little finger. (Fig. 170.) The thickened and sclerosed cusps may become calcified, so that the valve can neither open nor shut, a combined condition of stenosis and incompetence. The chordæ tendineæ may be so thickened and shortened that the papillary muscles seem to be implanted on the valve. There may be thrombus formation in the dilated left auricle, particularly in the auricular appendix. This is very important, because the clot may become detached and give rise to cerebral embolism. Moreover a thrombus often forms in the right auricle, and this may cause pulmonary embolism, especially when auricular fibrillation sets in. Thus, though in rheumatic endocarditis there are no friable vegetations which can become detached, yet embolism is a common complication of mitral stenosis. In rare cases a ball thrombus may be present, a large globular mass lying free in the auricle.

The *general effects* of mitral stenosis are those of chronic venous congestion. (See Chapter 3.) This is most marked in the lungs and liver. The distended pulmonary capillaries may rupture into the alveoli causing hemoptysis. Mitral stenosis is the commonest cause of hemoptysis or the

coughing up of blood. The common explanation for this is the distended condition of the pulmonary capillaries, but it seems more probable from the observations of Ferguson and his associates that the hemorrhage takes place from varicosities in the submucous bronchial veins. These workers by means of injection methods showed that there is a free communication between the main pulmonary veins and the bronchial veins, and that in mitral stenosis the latter veins become dilated and varicose. Areas of hemorrhage and infarction are common in the lungs, and there are great numbers of heart failure cells in the alveoli. Owing to extravasation of blood there is fibrosis of the septa, and the lung becomes brown and firm, a condition known as *brown induration*. The pulmonary artery and its branches often show marked atheroma owing to the continued strain though the aorta may be normal. The pulmonary arterioles may show a hyperplastic sclerosis and necrosis similar to that seen in the renal arterioles in malignant hypertension. Parker and Weiss point out that in severe cases of mitral stenosis there may be great thickening of the basement membrane

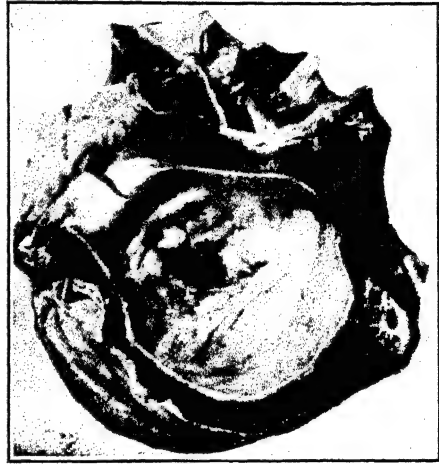


FIG. 170.—Mitral stenosis. The thickened cusps have fused so as to cause extreme narrowing of the opening.



supporting both the alveolar epithelium and the vascular endothelium, and that the space between them may become widened by edema, so that the alveolar tissue may be twenty times thicker than normal. As a result there is a grave interference with gaseous exchange, the blood being separated from the alveolar air by so thick a partition. This explains why it is that intense cyanosis may persist in spite of myocardial improvement. The liver shows marked congestion and may become indurated. The other organs are congested to a lesser degree.

**Mitral Incompetence.** The organic as opposed to the functional form of mitral incompetence is due either to sclerosis and contraction of the cusps or to dilatation of the ring. The common cause is rheumatic endocarditis. Subacute bacterial endocarditis will also cause incompetence because of the large vegetations, the sclerosis, and the occasional destruction of the cusps. In old age the cusps may undergo degeneration and calcification which will interfere with their efficiency. The condition of the heart is similar to that of mitral stenosis except that the left ventricle is also much dilated owing to the increased amount of blood which it has to accommodate. In the end-stages the heart is greatly enlarged.

**Aortic Incompetence.** The two principal causes of aortic incompetence are rheumatic endocarditis and syphilitic aortitis. Two additional causes are subacute bacterial endocarditis and the nodular sclerosis of old age. Incompetence due to endocarditis is caused by adhesions, thickening, and retraction of the cusps. It may be combined with stenosis, and is seldom so extreme as the incompetence caused by syphilis. In the syphilitic form the incompetence may be due to one or more of three factors: (1) dilatation of the aortic ring caused by destruction of the elastic tissue; (2) widening of the commissures; and (3) retraction of the cusps and thickening of their free edge. The dilatation may be so great that the valve becomes useless though the cusps may be healthy, and the incompetence is complete. High blood-pressure and severe physical strain naturally aggravate the condition. It is doubtful if atheromatous degeneration alone can cause incompetence, but the possibility cannot be denied.

The condition of the heart is the opposite of that of mitral stenosis. Here the heart is all left ventricle. It is extremely enlarged and globular in outline, the *cor bairinum*. The left ventricle is greatly hypertrophied as well as dilated. The condition of the aortic valve will depend entirely on whether the incompetence is endocardial or syphilitic in origin.

The *clinical picture* is highly characteristic, but is much more extreme in the syphilitic form. The symptoms and signs are due to the escape of blood from the aorta back through the incompetent valve. The arteries thus contain too much blood during systole and too little during diastole. This accounts for the leaping peripheral vessels ("the dance of the arteries"), the capillary pulsation, the water-hammer pulse (Corrigan pulse), the low diastolic pressure, and the high pulse-pressure, the giddiness and attacks of syncope due to cerebral anemia. The diastolic murmur which is the most characteristic physical sign is due to the blood escaping back into the ventricle.

**Aortic Stenosis.**—This is quite uncommon in a pure form, although in the rheumatic variety of aortic incompetence the rigid and adherent

cusps may be unable to open fully so that a relative degree of stenosis is produced. Pure aortic stenosis usually occurs in men over fifty years of age, and is of the *calcified nodular type*, best called *calcific aortic stenosis*. The cusps adhere together to form a kind of diaphragm as in mitral stenosis, but the most striking feature is the presence of warty calcified masses which may cover the cusps or be confined to the base. (Fig. 171.) The entire valve is incredibly hard and rigid. The calcification can be seen in roentgen-ray films. There is marked difference of opinion as to whether the lesion is rheumatic in origin or degenerative (arteriosclerotic) in character, the so-called Mönckeberg type. The fact that the condition is a clinical entity does not necessarily mean that it is an etiological entity, so that some cases may be rheumatic and others degenerative. Hall and Ichioka consider that all cases are rheumatic in origin, although the rheumatic lesions in the myocardium may be largely healed and hard to recognize. In their series of cases 60 per cent had solitary aortic lesions, while 40 per cent had healed mitral lesions. Karsner also believes that calcific sclerosis is essentially rheumatic in origin. It must be remembered that the stigmata of previous rheumatic disease can frequently be detected in any series of hearts which are examined with sufficient thoroughness, so that their presence in a case of calcific aortic stenosis is no proof that the latter lesion is rheumatic in origin. It seems probable that many cases should still be regarded as degenerative in nature, especially when the mitral valve is entirely normal.



FIG. 171.—Calcified aortic stenosis.

The heart shows a perfect example of pure or concentric hypertrophy of the left ventricle, although toward the end it may undergo dilatation. The average weight is about 650 grams, and in one of Christian's cases it weighed over 1000 grams. The aorta is remarkably smooth and free from atherosclerosis for patients over middle age, and it almost seems as if the vessel wall has been protected by the stenosis. As so little blood enters the aorta the pulse is small and fainting attacks are common. The pulse tracing with its slanting upstroke and rounded camel's hump speaks eloquently of the resistance at the aortic opening. The most characteristic physical sign is a rough rasping systolic murmur and thrill at the aortic area. If incompetence is also present, a diastolic murmur will be added.

**TRICUSPID STENOSIS.**—Rheumatic infection may spread from the mitral to the tricuspid valve ring, and the subsequent endocarditis may cause the leaflets to be glued together, with resulting stenosis.

**PULMONARY STENOSIS.** In most instances this lesion is congenital (developmental) in origin. The rare acquired cases are due to rheumatism.

## CHRONIC HEART FAILURE

The most common cause of death is failure of the heart. This may be slow or sudden. The three great causes of gradual failure are valvular disease, arteriosclerotic narrowing of the coronary arteries and arterial hypertension. We may therefore speak of valvular heart disease, arteriosclerotic heart disease, and hypertensive heart disease. Hypertensive heart disease is commoner than all the other forms put together.

In a pure obstructive lesion such as aortic stenosis the chamber proximal to the obstruction will undergo a work *hypertrophy*, the muscle fibers becoming larger but not more numerous. MacMahon, however, has shown that in idiopathic cardiac hypertrophy of infants true proliferation of the fibers may occur, and in rare instances the same is true of children after severe toxic injury to the heart. The best example is seen in the so-called *concentric hypertrophy* of the left ventricle in arterial hypertension, whether of the primary "essential" type or secondary to chronic nephritis. In arteriosclerotic heart disease there may or may not be hypertrophy, depending on whether there is or is not an associated hypertension.

In course of time *dilatation* is added to hypertrophy. This may be compensatory or may be due to failure. Compensatory dilatation is seen in aortic incompetence. During diastole the blood regurgitates from the aorta through the incompetent valve into the ventricle in addition to that entering it from the auricle. If venous congestion is to be avoided the ventricle must dilate. At the same time it hypertrophies in order to cope with the increased amount of blood it has to expel with each contraction.

Dilatation from failure is likely to be the end of every cardiac lesion if the patient lives long enough. For a time hypertrophy can look after the increased load, but there comes a time when the effort fails, the muscle becomes exhausted, and the cavity dilates. This is more apt to occur when the myocardium itself is not healthy, as from fatty degeneration or myocardial scarring. A healthy heart may be acutely dilated as the result of very great and sudden exertion. The cavities will gradually return to normal size with rest in bed, but there may be functional cardiac disability for some time.

Cardiac failure may be mainly left ventricular, or mainly right ventricular, or both. In chronic left ventricular failure the symptoms and signs are those of pulmonary hypertension with normal pressure in the systemic veins, *i. e.*, cardiac dyspnea and accentuated pulmonary second sound. Right ventricular failure follows upon prolonged pulmonary hypertension, which in turn may be due to left ventricular failure, to mitral stenosis, or to intrinsic pulmonary conditions. The term *cor pulmonale* is applied to a condition of enlarged right heart (first hypertrophy and later dilatation) and dilated pulmonary artery due to narrowing of pulmonary arterioles and the capillary bed by pulmonary fibrosis, emphysema, or (rarely) pulmonary endarteritis obliterans; silicosis is an important cause of vascular obstruction; chest deformities (spinal curvature, etc.) may cause mechanical obstruction. The final stage of cardiac failure is *congestive heart failure*, with engorged systemic veins, a large and tender liver, swollen legs, ascites, pleural effusion especially on the right side, and marked cyanosis.

In infectious diseases heart failure is a frequent cause of death, and at autopsy the heart is often found to be remarkably soft and flabby. This may be due in part to the action of toxins on the myocardium, but a major factor appears to be peripheral circulatory failure. The strength of the cardiac contraction depends on the

load placed on the muscle, and for a normal load there must be adequate filling of the ventricles during diastole and adequate venous flow from the periphery. If the blood collects in the dilated capillary plexuses in the viscera and skin in severe infections, shock, etc., or in the pulmonary vessels in influenza, the heart is not given enough work to do, loses its tone, and finally fails.

## LESIONS OF THE MYOCARDIUM

**TOXIC MYOCARDITIS.**—This is a degenerative condition rather than an inflammatory one. Diphtheria offers a good example. There is an acute degeneration of the muscle followed later by a secondary cellular inflammatory reaction. The muscle fibers are swollen and granular and have lost their striations. In septicemia and toxemia, even though no microscopic changes may be evident, the heart is often so flabby and lacking in tone that it flops down on the autopsy table. The *sulphonamide drugs* may cause an acute interstitial myocarditis both in man and in experimental animals. The exudate is rich in eosinophils.

**SUPPURATIVE MYOCARDITIS.**—This is usually a manifestation of pyemia, but the infection may spread from an acute ulcerative endocarditis or an acute pericarditis. Miliary abscesses are scattered through the fibrous tissue of the heart, or there may be a diffuse infiltration with polymorphonuclear leucocytes. There is marked destruction of the muscle fibers, and the condition ends in death.

**TUBERCULOUS MYOCARDITIS.**—This is very rare. There may be miliary tubercles scattered through the myocardium. Still more rarely there are large yellow caseous lesions of the myocardium unlike anything else found in the heart.

**SUBACUTE MYOCARDITIS OF UNKNOWN ETIOLOGY.**—There is a small group of obscure cases characterized by rapid myocardial failure or sudden death in which granulomatous or subacute inflammatory lesions are found in the myocardium. It is probable that they represent a heterogeneous collection and not a definite entity, so that no really satisfactory name has been suggested. It is reported in the literature under such names as idiopathic myocarditis, Fiedler's myocarditis (first reported by Fiedler in 1899), and isolated myocarditis. A good review of the subject is given by Magner, who reports a case from my laboratory. The patient had previously been in good health, and died unexpectedly after the removal of a non-toxic goiter; scattered through the myocardium were foci of mononuclears and giant cells. It seems probable that the causal agent is a virus, so that a good name might be virus myocarditis. Other viruses such as those of poliomyelitis (50 per cent) and varicella are known to produce similar myocardial lesions. Identical lesions due to a virus occur in the anthropoid ape (Schmidt).

**DEFICIENCY MYOCARDITIS.**—Vitamin deficiency may lead to myocardial failure associated with lesions in the heart muscle. *Beri-beri*, the oriental disease due to lack of vitamin B (thiamine) from eating polished rice, is marked by nervous and cardiovascular manifestations. It is coming to be recognized that an occidental form also exists, caused again by thiamine deficiency due, as a rule, to chronic alcoholism (Weiss and Wilkins). Other factors, at present unrecognized, must be necessary, for chronic alcoholism is very common, whilst *beri-beri* is rare. The condition of the heart varies to a bewildering degree. The heart may appear normal or may be dilated or hypertrophied and overweight. There may be no microscopic changes, but usually there is "hydropic" degeneration and vacuolation of the myocardial fibers including those of the subendocardial conduction system, (Fig. 172) edema of the interstitial tissue, and fibrosis in the later stages. The onset of symptoms of myocardial failure in an alcoholic addict may be sudden or gradual. The condition is relieved by the administration of thiamine. It may be noted that electrocardiographic changes develop in healthy volunteers on a thiamine deficient diet.

It sometimes happens that a person without any obvious history of vitamin deficiency dies with all the symptoms of chronic heart failure, but with no evidence of valvular disease, hypertension or coronary occlusion. The heart is greatly enlarged, being often double the normal weight. Here also there is evidence to suggest that some of these cases are due to dietary deficiency, possibly thiamine or some other member of the vitamin B complex (Dock, Smith and Furth). A striking feature may be great thickening of the endocardium with or without mural thrombosis. It is well known that the cardiac failure of beri-beri is associated with great hypertrophy and dilation of the heart, the so-called beri-beri heart.

**FATTY DEGENERATION.** This is caused by the usual factors responsible for fatty degeneration (see Chapter 2), of which severe anemia, especially the pernicious form, is the chief. In the gross the heart shows the characteristic mottled "thrush-breast" appearance, best seen under the endocardium covering the papillary muscles of the left ventricle (Fig. 180). The yellow spots represent areas of fatty change.



FIG. 172. Beri-beri heart.

Microscopically rows of fat droplets are seen in the muscle fibers in frozen sections; they can be stained red with Sudan III or Scharlach and black with osmic acid. Unless it is very extreme the condition does not seem to interfere seriously with the power of the heart. It frequently happens that if a heart which is very soft at autopsy is examined by frozen section and Sudan staining, widespread fatty degeneration will be found, even in the absence of the thrush-breast appearance, which is seldom seen apart from pernicious anemia.

**Sarcoidosis.** Sarcoidosis of the myocardium is a rare cause of acute heart failure. Very occasionally there may be chronic congestive failure. Most of the reported cases have been young male Negroes, but the two cases which I have examined have both been white. The myocardium is extensively replaced by sarcoid lesions, the giant cells of which often contain asteroid inclusions. In order to distinguish the condition

from tuberculoid reactions it is desirable to be able to demonstrate sarcoid lesions in lymphoid and other tissues. The sudden death is probably due to ventricular fibrillation or the Stokes-Adams syndrome caused by involvement of the conduction system.

**FATTY INFILTRATION.** This is a lipomatosis of the heart, with deposits of fat under the pericardium and in the interstitial tissue. (Fig. 173.) It is merely part of a general adiposity. The muscle fibers may suffer from pressure, and if the infiltration is very marked there may be interference with the heart's action.

**BROWN ATROPHY.** Here there is wasting of the heart, which is of a deep brown color. The condition is seen in long-continued wasting diseases and in old age. The muscle fibers are small, and at each pole of the nucleus there is a collection of yellow pigment, one of the lipochromes. This pigment has been well named a "wear-and-tear" pigment, for, although normally present in small amount, it becomes very greatly increased in conditions where the tissues undergo much wear and tear.

**FRAGMENTATION.**—In soft and flabby hearts, such as occur in continued infections, intestinal obstruction, etc., the muscle fibers may be fragmented, *i.e.*, broken across transversely, the broken ends being separated for some little distance (Fig. 174). Owing to the absence of any surrounding reaction to injury it is usually supposed that the condition develops in the death agony. It may occur in the healthy heart if death is violent (hanging, strychnine poisoning, etc.). In the latter cases there is likely to be a clean break and nothing more, whereas in the flabby hearts there is often an accompanying degeneration and disintegration of the muscle fibers.

**Hypertensive Heart Disease.**—The four principal forms of heart disease are those due to rheumatic fever, bacterial endocarditis, coronary artery occlusion, and arterial hypertension. The last of these is the commonest.



FIG. 173.—Fatty infiltration of heart.  $\times 125$ .



FIG. 174.—Fragmentation of myocardium.  $\times 250$ .

A person with hypertension may live for many years without showing any symptoms. During this time the heart is accommodating itself to the increased work it has to do. As the patient gets older, as the coronary arteries become narrowed, and particularly if the blood-pressure continues to rise, the day will come when the myocardium is no longer equal to the strain, and congestive heart failure develops.

The most striking feature is marked hypertrophy of the left ventricle, so that when the heart is grasped it feels like a closed fist. The walls are rigid, the heart maintaining its curved form when laid on the table. In the late stages dilatation may be added to the hypertrophy. Strands or patches of fibrous tissue are often scattered through the wall of the left ventricle.

Apart from this fibrosis, which may be minimal in degree, the heart muscle appears normal. The individual fibers show no sign of degeneration, and are frequently hypertrophied. Why they should fail remains a mys-

tery. What seems to be powerful muscle is unable to expel the blood from the heart with any vigor. It is evident that in the myocardium morphological appearance does not necessarily correspond with functional capacity.

## CORONARY ARTERY OCCLUSION

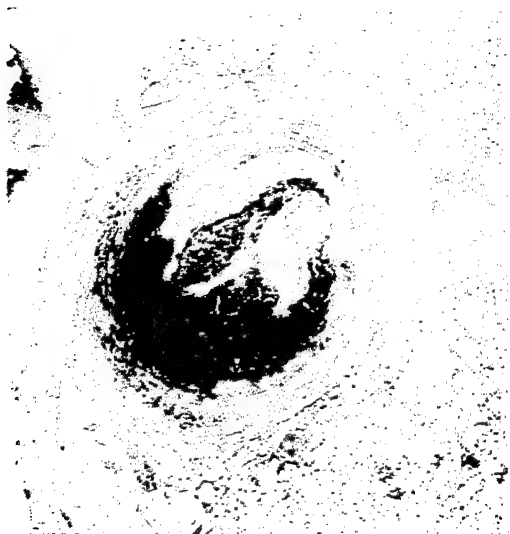
Three things may happen when one of the larger branches of the coronary arteries is occluded: (1) The patient may die immediately. By far the commonest cause of sudden death is cardiac failure; indeed it is the only thing which will kill a person *instantaneously*. The commonest cause of sudden cardiac failure is coronary occlusion. (2) He may linger for a few hours or days. (3) In many cases he recovers, at least for a time. Death from coronary occlusion is common among doctors and other professional men. Deaths from coronary disease appear to be increasing in frequency. The figures in round numbers for the United States were 28,000 in 1930, 101,000 in 1940, and 111,000 in 1942. The corresponding figures for England and Wales were 1,900 in 1926, 25,000 in 1945, and 33,000 in 1947.

*Pathogenesis.* Complete occlusion of a coronary artery may be produced in a variety of ways. (1) Atherosclerotic narrowing of the vessel with complete obstruction of the lumen. (2) Hemorrhage into an atheromatous plaque. (3) Rupture of such a plaque into the lumen. (4) Thrombosis in an already atheromatous artery. Rare causes are (5) syphilitic aortitis sealing the mouths of the coronaries and (6) an embolus from a vegetation on the aortic valve. When an embolus blocks a main coronary artery, death occurs with dramatic suddenness. Occasionally syphilitic arteritis of the coronary artery may cause occlusion. At the site of the atheromatous plaque numerous lymphocytes are sometimes present in the adventitia. This appearance must not be mistaken for the perivascular cellular infiltration characteristic of syphilis. Of these various causes by far the most important is atherosclerosis, with or without an added thrombosis. For this reason the general cardiac condition from which the patient suffers may be called *arteriosclerotic heart disease*. The coronary arteries share in the general atherosclerosis of old age. In young adults, however, the coronaries may be the only vessels affected, the condition being much more common in men than in women. Dock points out that the intima of the coronaries lying in the epicardium is much thicker than that of any artery of similar caliber elsewhere in the body, and that this is much more pronounced in the male, being present even in infants. This anatomical peculiarity may have some etiological significance.

Duguid suggests that some (he says many) of the lesions regarded as atheromatous are arterial thrombi which have been transformed into fibrous thickenings by the process of organization. Most of the thrombi consist of fibrin, and these are converted into fibrous patches which fuse with the intima and become covered by endothelium. When the thrombus contains large numbers of red blood cells, fatty degeneration occurs, this may give a picture indistinguishable from that of an atheromatous plaque.

The importance of hemorrhage into an atheromatous plaque in the intima was first pointed out by Paterson and later by Winternitz. The hemorrhage is due to rupture of capillaries caused by atheromatous softening. (Fig. 175.) In the majority of cases of coronary thrombosis intimal hemorrhage can be demonstrated, but numerous blocks and serial

PLATE VII



*Old Hemorrhage into Atherosclerotic Plaque.*

The hemosiderin is stained intensely with the Prussian blue method.



sections may be needed for this demonstration. Even without thrombosis the hemorrhage may produce great narrowing of the lumen by causing bulging of the intima (Plate VII). When hemorrhage is marked it can be recognized with the naked eye in cross-section of the artery. Intimal hemorrhage offers an explanation of those attacks of coronary occlusion which are precipitated by sudden exertion or excitement, both of which cause a temporary rise in the blood-pressure. When the coronary arteries of adults who die suddenly are examined by means of preliminary perfusion and fixation followed by dehydration and clearing, hemorrhages are found with remarkable frequency (Durlacher *et al.*). These are nearly always multiple, and vary in age from fresh extravasations to areas of iron-containing pigmentation. Thrombi are more frequently associated with older hemorrhages than with fresh ones. In more than one-half of the cases of acute occlusion the heart is enlarged (overweight), due possibly to hypertension, which may be an etiological factor. Some workers, however, believe that coronary arteriosclerosis may lead to cardiac hypertrophy quite independent of hypertension.

Occlusion may be caused by rupture of atheromatous material into the lumen. It will be realized by now that, contrary to common belief, thrombosis is not the invariable nor indeed the commonest cause of coronary occlusion and myocardial infarction. In my experience the chief causes in order of frequency are: (1) atheroma, (2) hemorrhage into the intima, (3) rupture of an atheromatous plaque, and (4) thrombosis.

The relation of hypertension to ischemic heart disease has long been a matter of debate. In support of such a relationship it can be pointed out that nearly 50 per cent of the ischemic cases have a blood pressure at least 160/100, and that at autopsy hypertrophied hearts often have atheromatous coronaries. The facts are undoubted, but the conclusion that they indicate a causal relationship is unwarranted for the following reasons. (1) Both hypertensive and ischemic heart disease are common at the same age period, and about half the population between the ages of fifty and sixty have blood pressures of 150/100. (2) Cardiac hypertrophy is not necessarily due to hypertension. Coronary sclerosis can also produce hypertrophy, as stretching of the heart by dilatation serves as a stimulus to hypertrophy. (3) Atheromatous coronary arteries do not necessarily indicate ischemia, for it is very difficult to determine the size of these vessels during life by the ordinary methods of the autopsy room. In order to circumvent this difficulty Harrison and Wood in a notable contribution to this contentious subject injected the coronary



FIG. 175.—Coronary capillary passing from lumen into wall.  $\times 160$ .

arteries with a radio-opaque gel at the known diastolic pressure of the patient and then cleared the whole heart so that the arteries were rendered visible. They arrived at the following conclusions: moderate degrees of coronary atheroma do not necessarily cause narrowing; the size of the coronaries during life varies directly with the heart weight; the arteries vary sharply between hypertensive and ischemic cases, in the former being large with smooth bore, in the latter being narrow and frequently occluded; in hypertensive cases the heart weight varies with the degree of failure during life and not with the height of the blood pressure; in ischemic cases cardiac hypertrophy is the rule and can be correlated with the duration of failure.

The *relation of trauma* to coronary thrombosis is difficult to decide. Many cases are reported in the literature where a non-penetrating injury to the precordia has been followed almost immediately by symptoms of thrombosis and infarction. In such cases it is reasonable to assume that trauma precipitated the thrombosis. The coronary artery is already the site of atheroma, and trauma may cause hemorrhage into an atheromatous plaque, thus initiating thrombosis.

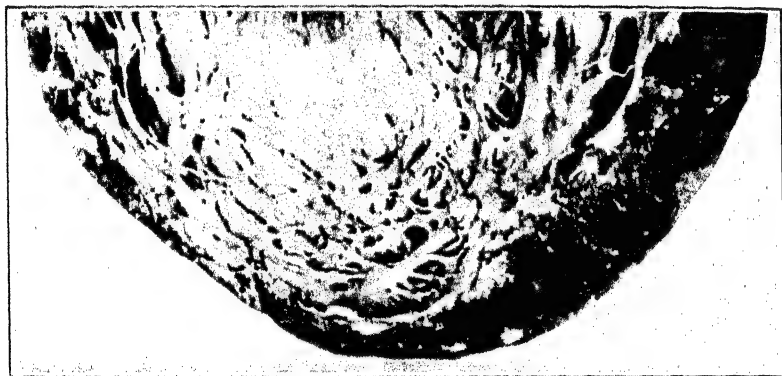


FIG. 176.—Myocardial fibrosis following infarct. The wall of the ventricle at one side and at the apex is markedly thinned.

**SYMPTOMS.** Parkinson remarks that when a man of advancing years is seized while at rest with severe pain across the sternum, which continues for hours and which is accompanied by shock, you may diagnose coronary occlusion. The chief incidence is between forty-five and sixty years of age. After sixty years the disease is not so common because of increasing anastomoses and vascularity in the myocardium of the left ventricle. Sudden death from extreme atheromatous occlusion of the coronary arteries may occur in the early twenties and thirties, as illustrated by the report of French and Dock on 80 cases in soldiers between the ages of twenty and thirty-six. The pain is abrupt in onset; the patient is well one minute and in agony the next. It is usually precordial but may be epigastric, and as there is often slight fever and a moderate leucocytosis, an acute abdominal condition is apt to be diagnosed. Newspaper accounts of death from acute indigestion are examples of coronary occlusion. Sometimes there is no pain. Dyspnea is the most constant symptom. The face is ashy pale and bathed in sweat. Shock is present, but is not to be explained by any of the current theories for traumatic shock. It is a manifestation of heart failure. There may be *angor animi*, a feeling of impending dissolution. Weak heart sounds, acute pulmonary edema, enlargement of the liver, and albuminuria are common features. There is an increase in the sedimentation rate, usually about the fourth or fifth day. A pericardial friction rub which is characteristically fleeting is often present. The *prognosis* varies. About one-half

PLATE VIII



Recent Infarct of Heart

The yellow necrotic tissue in wall of left ventricle is edged by a narrow dark red border.

die suddenly. Of the remainder about one-half make a complete functional recovery and are able to resume work. The other half develop congestive heart failure or anginal attacks.

The occlusion is usually in the anterior descending branch of the left coronary about 2 cm. from the commencement. Distal to the occlusion there may or may not be a thrombus. The atheromatous patch may block the lumen so completely that not even the finest probe can be passed along it. The result of acute occlusion, most readily understood when thrombosis completes the occlusion, is the production of a *myocardial infarct*. Of course, if the occlusion causes sudden death there will be no time for an infarct to be produced.

The area involved includes the anterior part of the interventricular septum, the apex, and the anterior part of the wall of the left ventricle. The papillary muscles suffer most severely. When the right coronary is occluded the infarct includes the posterior half of the interventricular septum and the posterior part of the wall of the left ventricle, with little or no involvement of the right ventricle. The immunity of the right ventricle to infarction may be due to the fact that the Thebesian vessels open almost entirely into that chamber, so that the wall of the right ventricle can receive blood from this collateral source. The areas are irregular in shape, yellow in color, and often surrounded by a red zone. (Plate VIII.) The larger areas may undergo softening (*myomalacia cordis*), and this may lead to rupture of the heart. If the endocardial surface is involved a thrombus will be formed on the necrotic area, and if the pericardial surface is involved there will be a patch of pericarditis. The area of pericarditis is more extensive than the apparent area of infarction. Embolism, sometimes fatal, may occur as a result of the mural thrombus becoming detached. There is a double threat of embolism in myocardial infarction, sys-

temic from the mural thrombus and pulmonary from venous thrombosis in the leg which may result from circulatory failure and confinement to bed. Gradually the infarct becomes replaced by fibrous tissue, so that it is represented by a white patch of scar visible both on the endocardial and on the cut surface with corresponding thinning of the wall of the ventricle. (Fig. 176.) Should the patient survive for some time the weakened area will give way and bulge outward, so that an *aneurism of the heart* is formed with marked



FIG. 177.—Aneurism of heart showing bulging and thinning of ventricular wall.

thinning of the wall. (Fig. 177). This usually involves the anterior wall of the left ventricle near the apex. In course of time this aneurism may rupture, causing sudden death. Rupture of the heart may, therefore, be the result of a recent infarct or of a cardiac aneurism. This is the only way in which a person may die of a broken heart. Sometimes a thrombus will form on an area of scarring, even though there is no recent necrosis. A heart which is the site of an old infarct is usually hypertrophied; in many cases this hypertrophy is not related to hypertension. Cardiac hypertrophy may be caused by anoxia of the myocardium. In transposition of the great vessels the coronary arteries arise from the pulmonary artery with resulting myocardial anoxia and marked hypertrophy of the left ventricle.



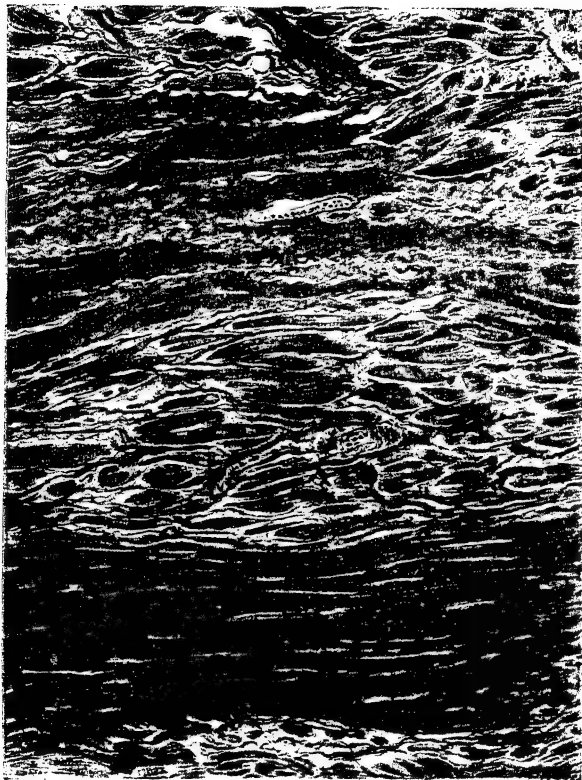
FIG. 178. Infarct of heart, early stage. The dark material represents normal muscle fibers, the pale areas are degenerated fibers.  $\times 200$ .



FIG. 179.—Healed infarct of heart.  $\times 140$ .

The *microscopic appearance* of the infarct depends on its age. The sequence of events was determined in the experimental animal by Karsner and Dwyer in 1916, and more recently in the human subject by Kenneth Mallory and his associates. Necrosis is not evident till the end of six hours, when the muscle fibers become hyaline and stain a deeper red with acid dyes. The striations are indistinct and finally lost, the clear outline of the fibers are now smudged, the spaces between the fibers are filled with granular debris, and the nuclei disappear. Some of the fibers may become swollen and vacuolated before disintegrating. (Fig. 178.) In the *first week* there is slight polymorphonuclear infiltration of the necrosed area at the end of twenty-four hours, and by the fourth day this has become marked. Removal of the necrosed tissue begins. In the *second week* this removal is

## PLATE IX



Fibrosis of the Myocardium, the Result of Coronary Occlusion.

The heart muscle is red, the fibrous tissue blue. (Mallory's connective tissue stain.)

carried out by great numbers of pigment-filled macrophages, which replace the polymorphonuclears. The pigment is partly muscle pigment and partly blood pigment resulting from hemorrhage from greatly distended vessels. New capillaries and fibroblasts grow into the infarcted area. In the *third week* removal of the dead muscle may be completed in small infarcts, though much delayed in large lesions. The fibroblasts begin to form collagen. From the *fourth* to the *sixth week* collagen formation is marked. (Plate IX.) By the *end of the second month* the process is complete and the infarct is healed. All the dead muscle is replaced by dense scar tissue, and only a few cells and granules of blood pigment remain. (Fig. 179.) The speed of the process varies with the size of the infarct and the state of the remaining circulation.

Gradual occlusion of the vessel will lead to the same end-result, *i. e.*, myocardial scarring, though without the production of an infarct. In this case the muscle fibers gradually die and are replaced by fibrous tissue, the condition inappropriately called chronic interstitial myocarditis. No blood pigment is found in these lesions. Fatty degeneration can be demonstrated in the slowly dying fibers; this is not the case in an infarct.

It not infrequently happens that in an autopsy on a person who has had no cardiac symptoms and who has died as the result of some other disease one is astonished to find the left coronary completely blocked by atheroma. The explanation is that a collateral circulation has slowly been established. The work of Blumgart and Schlesinger has demonstrated the part played by collateral vessels in a striking way. The coronary arteries were injected with a radio-opaque lead mass of different colors, followed by combined roentgenographic and dissection studies. The right artery was colored red and the left blue. Fine anastomoses less than 40 microns in diameter exist between the two sides, but these are of no functional value and do not permit passage of the injection mass. As the result of *slow* obstruction, abundant wide anastomoses develop, so that subsequent sudden obstruction may not result in infarction because the collateral circulation keeps alive the area deprived of its normal blood supply. This explains how it is that the site of an infarct does not necessarily bear a constant relation to the site of occlusion. This anastomotic circulation develops only where and when it is needed, either as a result of diminished coronary flow, or as a result of increased demand in a heart undergoing hypertrophy.

In rare cases there may be *infarction without coronary occlusion*. These cases, which are very puzzling, must be attributed to *relative* myocardial ischemia, which may be only temporary. In most of the cases hypertension has been present, a condition in which vasoconstrictor phenomena are common, and in which there is myocardial hypertrophy with a correspondingly increased demand for blood. There may be a temporary fall of the intra-aortic blood-pressure, or failure of the mechanism regulating compensatory dilatation of the coronaries. Finally, the pathologist may have failed to demonstrate occlusion of one of the smaller arteries. When the coronary vessels are examined by the combined injection-dissection technic it is found that almost two-thirds of the occlusions are less than 5 mm. long (Schlesinger and Zoll). Such short occlusions are easily overlooked.

RELATION OF SYMPTOMS TO LESIONS.—The sudden pain, distress, dyspnea, angor animi are due to the heart having received a sudden trauma from the cutting-off of the blood supply to part of the muscle. When any muscle is suddenly deprived of its blood supply as by embolism it goes into a painful spasm. An ordinary muscle can be rested, but the heart cannot afford to stop and rest. The leucocytosis is due to the formation of what is practically an aseptic abscess in the heart. The fever

is probably in the nature of a protein reaction from the dead tissue. The pericardial friction rub is due to the presence of a patch of aseptic inflammation caused by necrosis of the muscle on the surface of the left ventricle. It is not heard in occlusion of the right coronary artery, as the affected area is on the posterior surface of the heart.

There is a growing feeling amongst clinicians that there may be some connection between gall-bladder infection and coronary thrombosis. Patients with gall-bladder disease may show symptoms of early cardiac failure or angina pectoris. There may be only symptoms or definite cardiac lesions may be present.

**ANGINA PECTORIS.** Angina pectoris or sudden pain in the chest is a clinical rather than a pathological entity. In its typical form it differs sharply from the clinical picture of acute coronary occlusion, for the pain in angina comes on as the result of sudden exertion or emotional excitement and goes off when this has passed,



FIG. 180. Fatty degeneration of the heart. The "thrush breast" appearance is well shown. From a case of profound anemia.

it tends to pass down the arms, particularly the left, and there is none of the fever and leucocytosis of infarction of the heart. In many cases, however, the pictures come closer together, and a person may have a number of attacks of angina pectoris and finally die of coronary occlusion. The patient may die in the first attack as in the case of Dr. Arnold of Rugby, or he may have many attacks as did John Hunter, who described one of these in the following vivid words: "As I was walking about the room I cast my eyes on a looking-glass and observed my countenance pale, my lips white, and I had the appearance of a dead man looking at himself."

It is generally believed that the pain is due to temporary myocardial ischemia, the attack being brought on by physical exertion or emotional excitement which throw an additional strain on the heart. The ischemia is relative, and may be caused not only by coronary atheroma, syphilitic aortitis, aortic stenosis, etc., but also by cardiac hypertrophy without a corresponding increase in the coronary cir-



culation. It is evident that anginal attacks may finally terminate in cardiac infarction.

**CORONARY ARTERY CALCIFICATION IN INFANCY.**—A puzzling condition is the occurrence of extensive calcification of the coronaries in infants leading to death in a few days or weeks. It has been reported in the stillborn. There may be some biochemical disturbance of the ground substance or the elastica, or the calcification might be metastatic. There is no evidence of preëxisting arterial disease, bone disease, hyperparathyroidism, chronic renal disease, nor hypervitaminosis D. The condition may occur in siblings, and there may be calcification of the arteries in the brain, lungs and abdominal viscera, and in the aorta and myocardium.

**SUDDEN CARDIAC DEATH.**—When a person dies suddenly of heart failure (instantaneously or in the course of a few minutes or hours), the cause may lie in the myocardium, the coronary arteries, or the aorta. (1) There may be rupture of the heart due either to softening of an infarct or to the formation of an aneurism of the heart at the site of a scar. Sudden death on exertion may follow the myocardial degeneration of diphtheria. (2) Coronary occlusion is the commonest cause of sudden cardiac death. The occlusion may be at the mouth of the artery as in syphilitic



FIG. 181.—Myxoma of heart growing from wall of left auricle.

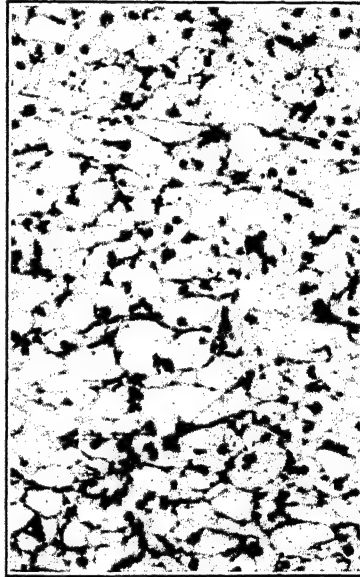


FIG. 182.—Glycogenic tumor of heart.  
× 165.

aortitis, or in the course of the artery as in atheroma. (3) In the aortic group may be placed rupture of an aortic aneurism, some cases of angina pectoris, and aortic incompetence. Finally there remains a group of cases in which the patient dies of sudden heart failure, but no satisfactory cause can be found at autopsy. Such cases may be put down to shock, status lymphaticus, or a visitation from God.

In relation to the last group the extensive experimental and clinical observations of Raab merit consideration. This worker suggests that many cases of myocardial failure and sudden cardiac death are not due to mechanical factors such as coronary occlusion or arterial hypertension but to an accumulation in the heart muscle of epinephrine, which is capable of causing myocardial anoxia as a specific metabolic effect. The epinephrine may be either discharged in excess (pheochromocytoma, angina pectoris without coronary disease, sudden cardiac death without adequate lesions), or excessively activated (thyrotoxic heart). Such a concept might serve

to explain many cardiac puzzles where the lesions found at autopsy fail to agree with the clinical picture observed during life.

**TRAUMATIC INJURY.** Nonpenetrating injuries to the heart may result in a variety of lesions. There may be partial or complete laceration of the myocardium. In the former case rupture may occur some days later. The trauma may produce infarction due either to coronary angiospasm or to hemorrhage into an atheromatous patch in the intima of a coronary artery with consequent thrombosis. Pericardial effusion may occur, and even subsequent constrictive pericarditis has been reported. In occasional cases a blow to the chest has resulted in death, although autopsy failed to reveal any structural damage to the heart. The importance of the subject from the medicolegal and compensation standpoint is obvious.

**TUMORS OF THE HEART.** Primary tumors of the heart are very rare, and need only be mentioned. Myxoma is a soft pedunculated tumor growing from the wall of the left auricle at the site of the closed foramen ovale. (Fig. 181.) The surface may be papillary in character. The microscopic picture is myxomatous, but may suggest that the tumor is really an endothelioma. Fibroma, angioma, and rhabdomyoma have been described. The so-called rhabdomyoma is better named *congenital glycogenic tumor* of the heart (Batchelor and Maun). It presents a characteristic vacuolated appearance due to great accumulation of glycogen in the tumor cells. (Fig. 182.) These tumors are seen chiefly in infants and the newborn. They are really developmental tumors, and are often associated with tuberous sclerosis of the brain and developmental defects in the kidneys.

## CONGENITAL HEART DISEASE

A great variety of congenital abnormalities of the heart may occur, some very rare, others incompatible with life, *e. g.*, absence of the heart, ectopia cordis, displacement of the heart in the neck or the abdomen, etc. There may be minor defects such as a lacunar fenestration of the semilunar valves, which are of no functional significance. Only the commoner conditions will be touched on here. For a fuller account the writings of Maude Abbott and the book of Helen Taussig should be consulted.

The key to most of the defects lies in variations in the formation of the septum which divides the heart into a right and left side. The primitive heart consists of three chambers, auricle, ventricle, and aortic bulb. Separate septa are formed which divide these chambers longitudinally into right and left sides, and subsequently fuse. If anything goes wrong with this fusion, congenital defects will result.

While the septum which divides the aortic bulb into aorta and pulmonary artery is being formed, a spiral twisting occurs so that the pulmonary artery moves forward and to the right, the aorta backward and to the left. If this twisting does not take place the aorta will rise from the right ventricle and the pulmonary artery from the left. This condition is known as *transposition of the great vessels*.

Much commoner is a *deviation of the septum*, nearly always to the right, so that the pulmonary artery is narrower and the aorta wider than normal. In this way pulmonary stenosis is produced. The bulbar septum is now unable to fuse with the ventricular septum, and the root of the aorta is astride the latter so as to arise partly from the left and partly from the right ventricle. A gap remains in the upper or membranous part of the interventricular septum.

Even if the deviation of the bulbar septum is not sufficient to bring the aortic opening astride the ventricular septum, the upper part of that septum will still tend to remain open, for the narrowing of the pulmonary opening raises the pressure within the right ventricle so that the blood tends to flow from it into the left ventricle, thus interfering with the closure of the opening in the interventricular septum. The same holds true for closure of the interauricular septum and the ductus arteriosus which connects the pulmonary artery with the aorta in intra-uterine life. It is for this reason that pulmonary stenosis is so often associated with other congenital cardiac defects. Deviation of the septum to the left will cause stenosis of the aortic opening, a much rarer condition.

About the only fact of importance known about the *pathogenesis* of congenital heart disease is the relation to maternal rubella in early pregnancy. The virus of German measles is apparently able to pass through the placental barrier in the earlier three months of pregnancy and to damage early somatic fetal development; passage in the later months can occur, but is much less frequent. Other common anomalies resulting from maternal rubella are ocular defects, deafness, and mental retardation. It would appear that if a woman contracts rubella in the first two months of pregnancy the chances of her child being born defective are about 100 per cent; if she contracts the disease in the third month the chances are about 50 per cent; whereas later in pregnancy the chances are very low.

The all-important feature of congenital heart disease is the possibility of an intermingling of the blood in the systemic and pulmonary circulations as the result of an arteriovenous shunt. The three common causes of left-to-right shunts are patent ductus arteriosus, auricular septal defect and ventricular septal defect. In all of these the lungs become overloaded with blood. An equally important clinical distinction is between cases with cyanosis and without cyanosis. Cyanosis will be caused by a right-to-left venous-arterial shunt, because venous blood then enters the systemic circulation. As the pressure on the left side is normally higher than on the right, special complicating conditions are necessary for the flow to be reversed. By far the most important of these is pulmonary stenosis, in which too little venous blood goes to the lungs and too much goes to the left side of the heart. The flow through a septal defect may originally be from left to right, but when the left ventricle begins to fail the direction of flow may be reversed. It is, therefore, important to differentiate between cyanosis which has been present since birth (blue baby) and cyanosis which has developed only when cardiac failure has set in. Apart from cardiac failure, even the most extreme degree of cyanosis is not associated with edema, a highly characteristic feature.

Congenital defects are points of weakness against bacterial infection. Not infrequently the patient with congenital heart disease dies of subacute bacterial endocarditis. The vegetations may be found on a bicuspid aortic valve, a stenosed pulmonary valve, or at the site of coarctation of the aorta.

At least 90 per cent of the patients with congenital disease of the heart and great vessels fall into one of four groups. These are, in their order of frequency: septal defects, coarctation of the aorta, patent ductus arterio-

sus, and the tetralogy of Fallot. The last three are amenable to surgical treatment.

**Pulmonary Stenosis.** This is the most important of the congenital heart lesions. Though associated with marked cyanosis the condition is compatible with fairly long duration of life. The opening is narrowed, and in addition the cusps are commonly fused together to form a diaphragm in the center of which there is a circular opening. The valve is usually sclerosed, but may be of normal thickness. Instead of three cusps there may be two or four. The wall of the right ventricle shows a marked work hypertrophy. In rare cases the stenosis may be either proximal or distal to the valve. The condition may be associated with patent foramen ovale, deficient interventricular septum, and patent ductus arteriosus. The usual cause of the condition is a deviation of the bulbar septum to the right, so that an unduly small pulmonary artery is cut off from an unduly large aorta with the production of the *tetralogy of Fallot*, i. e., pulmonary stenosis, displacement of the aorta to the right, enlargement of the right ventricle, and a defect in the interventricular septum. About 75 per cent of blue babies (congenital heart disease with cyanosis) are examples of the tetralogy of Fallot. It is possible, though by no means certain, that a small number of cases are due to fetal endocarditis. Those cases in which the valves are sclerosed and adherent, but without any accompanying displacement of the aorta or defect in the interventricular septum, may be inflammatory rather than developmental in origin. The *Eisenmenger complex* is a rare variation of the tetralogy of Fallot without pulmonary stenosis. The blood from the left ventricle is thus able to pour directly into the pulmonary artery, as a result of which that artery may be markedly dilated whilst the aorta is smaller than normal, changes which are readily detected by the roentgenologist. Cyanosis is late and slight. Pulmonary hypertension is marked, which explains the atherosclerosis in the pulmonary artery and the muscular hyperplasia and necrotising arteritis which develop in its branches (Old and Russell).

The diagnosis of pulmonary stenosis can now be made during life with a high degree of accuracy. In addition to such features as marked cyanosis (the classical "blue baby"), compensatory polycythemia, low oxygen content of the peripheral blood, and severe dyspnea, the roentgenogram reveals the small size of the pulmonary artery.

From what has already been said it is evident that the condition of the ductus arteriosus is all-important, for it is by this route that the lungs receive their main blood supply. If partial closure of the ductus occurs, the condition of the child may become extreme or desperate. For the relief of such a condition Blalock and Taussig have devised an operation which has succeeded in restoring the circulation to normal and the child to health. The principle is to bypass the obstruction by constructing an artificial ductus arteriosus, so that an adequate supply of blood is poured into the pulmonary circulation. This is done by anastomosing the innominate or left subclavian artery to the right or left pulmonary artery just distal to the bifurcation of the main artery in such a way that the blood flows to both lungs. In many instances the most dramatic improvement has resulted. The most suitable cases are those presenting the tetralogy of

Fallot with a small or closed ductus. Owing probably to the polycythemia there is a marked tendency to thrombosis, particularly in the cerebral vessels, and this may lead to a fatal termination after, and occasionally before, operation. Widespread thrombosis of the smallest pulmonary vessels is extremely common, and may well add to the difficulty of oxygenation (Rich). These thrombi may become organized.

**AORTIC VALVE LESIONS.**—Aortic stenosis is much less common than pulmonary stenosis. Apart from stenosis there may be an abnormal number of cusps, two or four. A bicuspid aortic valve is peculiarly liable to suffer from subacute bacterial endocarditis. Gross points out that if a bicuspid aortic valve is really congenital in nature it will be associated with other developmental cardiac defects; such cases are usually seen in children. In adults the condition is usually acquired in nature, rheumatic in origin, and not associated with other defects.

**Coarctation of the Aorta.**—This is a condition of narrowing of the aorta (*coarctare*, to press together) in the region where it is joined by the ductus arteriosus. Two forms are recognized, the infantile and adult, depending on the relation of the constriction to the ductus. In the *infantile type* the constriction is proximal to the ductus, between it and the subclavian artery, and the ductus remains widely patent. Other cardiac anomalies are common in this form. In the *adult type* the constriction is at or just distal to the ductus, which is obliterated. Other anomalies are rare, but subacute bacterial endocarditis is a common cause of death. The infantile form is not compatible with continued life, and is found in the still-born and young infants. The narrowing may be so great that the opening may barely admit a probe. In the adult form the blood makes its way to the lower part of the body by means of greatly dilated collateral vessels, the subscapular and internal mammary arteries from the subclavian anastomosing with the intercostals and epigastrics respectively. (Fig. 183.) This collateral circulation fails to develop in the infantile type, as the blood from the patent ductus enters the aorta beyond the obstruction. The *clinical picture* is characteristic, *i. e.*, arterial hypertension in the upper part of the body, large pulse volume in the arm and small in the leg, palpable or visible vessels along the dorsal border and angle of the scapula (subscapular collaterals), and a grooving of the ribs in the roentgen-ray film (internal mammary and intercostals).

It is now possible to excise the stenosed segment and join the divided ends, or even to insert an aortic graft. After this surgical *tour de force* the clamps on the aorta must be released gradually, otherwise the sudden release of pressure may lead to fatal fibrillation of the left ventricle.

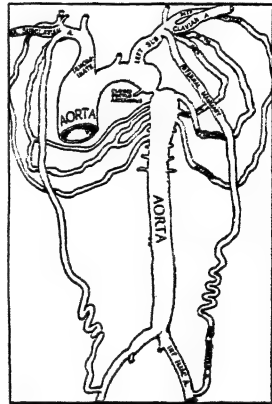


FIG. 183. —Coarctation of aorta with collateral circulation. (Maude Abbott and Dawson, International Clinics, courtesy of J.B. Lippincott Company.)

**Patent Ductus Arteriosus.** The ductus arteriosus is the channel by which in intra-uterine life the blood passes from the right heart into the aorta without passing through the lungs. It arises at the bifurcation of the pulmonary artery and ends in the aorta beyond the opening of the left subclavian artery. It is patent at birth, but becomes obliterated during the third and fourth weeks of extra-uterine life. It often remains open as the result of other congenital defects.

When the ductus remains patent, a condition which is twice as common in females as in males, the blood flows from the aorta into the pulmonary artery. In uncomplicated cases, therefore, there is no cyanosis. There may, however, be a temporary reversal of flow owing to heightened pulmonary pressure, as in prolonged crying, violent physical exertion, or terminal heart failure, with resulting cyanosis. If the ductus is acting as a compensatory mechanism to other congenital cardiac anomalies, cyanosis may be present even under resting conditions. There may be a rumbling systolic murmur and thrill in the pulmonary area. It is possible to pass a tube into a vein in the arm, and onwards into the jugular vein, right auricle and ventricle, finally entering the pulmonary artery. By this means the pressure effect of the flow of arterial blood into the pulmonary artery can be demonstrated and the increased oxygen content of the blood can be determined, so that the diagnosis can be confirmed with absolute certainty.

Although the condition is compatible with a long and active life, in the great majority of cases life expectation is considerably shortened. The great danger is the development of *Streptococcus viridans* endarteritis. This threat can now be averted by ligation of the ductus, or even better, by complete division.

**Auricular Septal Defects.** — Patency of the foramen ovale is the commonest and the least important of all congenital cardiac anomalies. The foramen remains patent in about 25 per cent of normal persons, but, as the opening is usually very small and oblique or valvular, little blood can pass from one side to the other.

A true septal defect due to failure of development is quite another matter. The opening may be very large. I have seen one 5 cm. in diameter in a middle-aged woman, and in such cases there may be a trilobular heart with what amounts to one auricle and two ventricles. The proportion of females to males is four to one. Blood passes so readily from the left side of the heart to the right that both the right auricle and the right ventricle become greatly dilated and hypertrophied. The large volume of blood which is pumped so continuously into the pulmonary artery leads to a remarkable degree of dilatation of that vessel, and atherosclerosis may be marked in it and in its branches. The aorta is small and hypoplastic. Twice as much blood may pass through the pulmonary as through the systemic circulation. For this reason there will be no cyanosis until cardiac failure sets in, and the patient may live from thirty to fifty years. Paradoxical embolism may occur through the large opening in the septum (Fig. 31, page 68). The diagnosis can be made with accuracy from the loud pulmonary systolic murmur caused by blood rushing into the dilated pulmonary artery, the large pulmonary artery shadow and the small

aortic shadow in the x-ray film, and marked right axis deviation in a person in fairly good health except for dyspnea.

The *Lutembacher syndrome* is a variant of auricular septal defect with the addition of rheumatic valvular disease, either stenosis or incompetence. The left auricle remains small owing to the bypass through the defect, in striking contrast to what is found in ordinary mitral stenosis. The pulmonary artery is again dilated.

**Ventricular Septal Defects.**—An uncomplicated defect of the ventricular septum is known as *Roger's disease*. The opening is usually small, situated in the membranous part of the septum, and causes little disturbance. It may, however, be much larger and in some cases there is complete absence of the septum, so that the heart has one ventricle and two auricles. Right ventricular hypertrophy, dilatation and failure will result, but here again cyanosis will be absent except as a terminal phenomenon. When associated with pulmonary stenosis, as in the tetralogy of Fallot, cyanosis will be the dominant feature, because now the shunt will be from right to left.

**ENDOCARDIAL FIBROELASTOSIS.**—This peculiar and rare lesion of infants is characterized by marked thickening of the endocardium of the entire left and occasionally the right ventricle, so that it has a white, thick, opaque appearance. In addition there is a remarkable enlargement of the heart, which may be several times the normal weight with dilatation of the ventricle. The thickening of the endocardium is due to proliferation of fibrous and connective tissue. The clinical picture is that of congestive heart failure ending in death. The condition always occurs in hearts with associated malformations which would produce endocardial anoxia, such as an anomaly of the coronary vessels, valvular atresia with stagnation anoxia, and premature closure of the foramen ovale which prevents the flow of oxygenated blood into the left ventricle before birth (Johnson).

**RELATION OF SYMPTOMS TO LESIONS.**—If there is cyanosis it may be present at birth ("blue baby"), or may develop later. It is due to the venous blood on the right side mixing with the arterial blood on the left. A compensatory polycythemia or increase in the number of the red blood cells takes place so as to compensate for the deficiency of oxygen. The size of the erythrocytes is also increased, so as to average 8 microns or more. Dyspnea is a common symptom due to deficient oxygenation. The patient is small and puny. There is clubbing of the fingers, as often happens in conditions of poor oxygenation; the terminal phalanges are thickened and the nails thick and curved. Various murmurs and thrills may be detected, but none are pathognomonic. The absence of pulsation in the lower extremities in coarctation of the aorta is very characteristic. An occasional complication is metastatic brain abscess, usually occurring in the tetralogy of Fallot. The abscess is nearly always single. The septal defect apparently permits a short circuiting of the circulation through the lungs, so that organisms may reach the cerebral circulation, although why abscess formation should be limited to the brain and to only one spot in the brain remains a mystery.

## THE PERICARDIUM

**Pericarditis.**—Inflammation of the pericardium is usually rheumatic in origin, and forms part of a rheumatic carditis. The pneumococcus is the next commonest cause, spreading from a pneumonic lung to the pericardium by way of the lymphatics. It may occur as a complication in septicemia or any of the infectious fevers. The tubercle bacillus may be the infecting

agent. Finally it may be a terminal condition in chronic debilitating diseases, particularly Bright's disease (uremic pericarditis).

**SYMPTOMS.**—The chief clinical features are fever, precordial pain, and a friction rub which at first may be soft like the rustling of silk, but later is rough and rasping like the creaking of leather. No acute infection may be more insidious in onset than pericarditis, and there may be no fever, no pain, no friction. Often the condition is discovered for the first time at autopsy, to the great surprise of the clinician.



FIG. 184. —Acute pericarditis. The shaggy nature of the exudate is well shown.

**LESIONS.**—The pericardium shows the usual characteristics of inflammation of a serous membrane. A thick fibrinous deposit is laid down on both the visceral and parietal layers, giving the heart a shaggy ("bread-and-butter") appearance. (Fig. 184.) Its gross and microscopic characters have already been described in connection with rheumatic heart disease. There is a varying amount of serous exudate, scanty in the rheumatic form but abundant and sometimes purulent in pneumococcal and other infections. The fluid collects first at the base of the heart. The fibrinous exudate may be largely absorbed, but some of it may be organized by the ingrowth of fibroblasts, and opaque white patches or *milk-spots* are left usually on the anterior surface of the right ventricle. Organization of the exudate may lead to the formation of adhesions between the two surfaces, and these



may involve the whole heart, a condition known as adherent pericardium. Calcification may occur in the organized tissue with the formation of stony plates on the surface of the heart.

**RELATION OF SYMPTOMS TO LESIONS.**—The most characteristic physical sign, the friction rub, is due to the two roughened surfaces rubbing against one another. If fluid accumulates to any extent the surfaces may be separated and the friction disappears. If the fluid is very abundant the heart sounds will be faint and distant. The pain is due to the same cause as the friction, the rubbing together of the inflamed surfaces. It may be slight or absent, and disappears as the fluid accumulates.

**TUBERCULOUS PERICARDITIS.**—The heart is usually covered with a fibrinous exudate which completely conceals the tubercles. The effusion is generally very abundant and purulent. If a pericardial sac is distended with pus, the condition is likely to be tuberculous or pneumococcal. Hemorrhage is common. A bloody exudate should suggest either tuberculosis or malignant disease. Microscopically the characteristic tubercles are seen under the fibrinous exudate.

**UREMIC PERICARDITIS.**—In persons dying of uremia a thin layer of fibrinous material may cover the pericardial surface. This contains urea crystals, as can be demonstrated in the autopsy room by means of the xanthydrol reaction.

**CHRONIC CONSTRICTIVE PERICARDITIS.**—In this uncommon condition the heart is compressed by a layer of dense tough fibrous tissue which envelops the organ. There is great uncertainty as to the cause of the dense envelope. Rheumatism can be ruled out. The thick, dense envelope may present large cavities containing inspissated caseous material. The tissue is hyalinized, any collagen fibers are huge, calcification is common, and tissue destruction is marked. It seems probable that most cases are tuberculous, although complete healing may have occurred.

The compression prevents the normal diastolic filling of the auricles, so that there is marked distention of the jugular veins, marked enlargement of the liver and recurring ascites. The heart, although profoundly disabled, is characteristically small and quiet, because it is unable to dilate or hypertrophy. The liver and spleen may be coated with a layer at first fibrinous and later fibrous, the so-called sugar-icing (Zuckerguss). This is apparently due to the long-standing ascites. The pleura may be similarly involved. This polyserositis has been called Pick's disease. Resection of the thickened and constricting pericardium has given excellent results in many cases.

**HEMOPERICARDIUM.**—Hemorrhage into the pericardial sac may be due to rupture of the heart, wounds of the heart, or rupture of an aneurism of the first part of the thoracic aorta. If the hemorrhage is rapid it will compress the auricles so that they cannot be filled, and death occurs from heart failure. If the hemorrhage is only a slow leak the heart may accommodate itself to the pressure. Blood is often found in the fluid exudate in tuberculous pericarditis and in effusion due to secondary tumors of the pericardium. Petechial hemorrhages in the serous membrane are common in septicemic and anemic conditions.

**HYDROPERICARDIUM.**—This is a dropsy of the pericardial sac, usually part of a general dropsy due to cardiac or renal disease. The sac may be greatly distended with clear watery fluid, which may interfere seriously with the heart's action.

#### ADDITIONAL READING

**Adrenalin and Sudden Death.** RAAB: *Ann. Int. Med.*, 1948, **28**, 1010.

**Anitschkow Cell.** CLAWSON: *Arch. Path.*, 1941, **32**, 760.

**Atypical Verrucous Endocarditis.** GROSS: *Am. J. Path.*, 1940, **16**, 375. KLEMPERER, *et al.*: *Arch. Path.*, 1941, **32**, 569. LIBMAN: *Tr. Assn. Am. Phys.*, 1938, **53**, 345.

LIBMAN AND SACKS: *Arch. Int. Med.*, 1924, **33**, 701.

- Bicuspid Aortic Valve.** GROSS: *Arch. Path.*, 1937, **23**, 350.
- Calcific Aortic Stenosis.** CHRISTIAN: *J. A. M. A.*, 1931, **97**, 158. CLAWSON, *et al.*: *Am. Heart J.*, 1938, **15**, 58. HALL AND ICHIOKA: *Am. J. Path.*, 1940, **16**, 761. KARSNER AND KOLETSKY: *Calcific Disease of the Aortic Valve*, Phila., 1947. SOPHAN: *Am. J. Med. Sci.*, 1945, **210**, 644.
- Chronic Adhesive Pericarditis.** WHITE: *Lancet*, 1935, **2**, 539, 597.
- Congenital Heart Disease.** Atlas of Congenital Cardiac Disease, New York, 1936. TAUSSIG: *Congenital Malformations of the Heart*, New York, 1947.
- Congenital Pulmonary Stenosis.** BEALOCK AND TAUSSIG: *J. A. M. A.*, 1945, **128**, 189. RICH: *Bull. Johns Hopkins Hosp.*, 1948, **82**, 389.
- Coronary Artery Calcification.** FIELD: *Arch. Path.*, 1946, **42**, 667. MENTEN AND FETTERMAN: *Am. J. Clin. Path.*, 1948, **18**, 805. SLADDEN: *J. Clin. Path.* 1952, **5**, 174. STRYKER: *Am. J. Path.*, 1946, **22**, 1007.
- Coronary Collateral Circulation.** BLUMGART, *et al.*: *Am. Heart J.*, 1940, **19**, 1.
- Coronary Embolism.** HAMMAN: *Am. Heart J.*, 1941, **21**, 401.
- Coronary Insufficiency.** GROSS AND STERNBERG: *Arch. Int. Med.*, 1939, **64**, 249.
- Coronary Occlusion.** BLUMGART, *et al.*: *Am. Heart J.*, 1940, **19**, 1. DOCK: *J. A. M. A.*, 1946, **131**, 875. DUGUID: *J. Path. and Bact.*, 1946, **58**, 207. DURLACHER *et al.*: *Am. J. Path.*, 1953, **29**, 588. FRENCH AND DOCK: *J. A. M. A.*, 1944, **124**, 1233. HERRICK: *J. A. M. A.*, 1912, **59**, 2015. HORN AND FINKELSTEIN: *Am. Heart J.*, 1940, **19**, 655. NELSON: *J. Path. and Bact.*, 1941, **53**, 105. PETERSON: *Arch. Path.*, 1938, **25**, 474. SCHLESINGER AND ZOLL: *Arch. Path.*, 1941, **32**, 178. WINTERNITZ, *et al.*: *The Biology of Arteriosclerosis*, Springfield, Ill., 1938.
- Coronary Thrombosis and Trauma.** BOAS: *J. A. M. A.*, 1939, **112**, 1887.
- Deficiency Myocarditis.** DOCK: *Trans. Ass. Am. Phys.*, 1940, **55**, 61. SMITH AND FURTH: *Arch. Int. Med.*, 1943, **71**, 602.
- Eisenmenger Complex.** OLD AND RUSSELL: *Am. J. Path.*, 1950, **26**, 789.
- Endocardial Fibroelastosis.** JOHNSON: *Am. J. Path.*, 1952, **28**, 566.
- General References.** VAQUEZ: *Diseases of the Heart* (English translation), Philadelphia, 1924. WHITE: *Heart Disease*, New York, 1951.
- Heart in Vitamin Deficiency.** THOMAS, *et al.*: *Yale J. Biol. and Med.*, 1940 **12**, 345. WEISS AND WILKINS: *Ann. Int. Med.*, 1937, **11**, 101.
- Hypertrophy of Heart.** MACMAHON: *Am. J. Path.*, 1937, **13**, 845.
- Infarct of Heart.** KARSNER AND DWYER: *J. Med. Res.*, 1916, **34**, 21. MALLORY, *et al.*: *Am. Heart J.*, 1939, **18**, 647.
- Mitral Stenosis.** FERGUSON, *et al.*: *Am. Heart J.*, 1944, **28**, 445. PARKER AND WEISS: *Am. J. Path.*, 1936, **12**, 573.
- Myocarditis.** SAPHIR: *Arch. Path.*, 1941, **32**, 1000; 1942, **33**, 88.
- Myxoma of Heart.** ORR: *J. Path. and Bact.*, 1942, **54**, 125.
- Nonbacterial Thrombotic Endocarditis.** ALLEN AND SIROTA: *Am. J. Path.*, 1944, **20**, 1025. ANGERIST AND MARQUISS: *Am. J. Path.*, 1953, **29**, 594. GROSS AND FRIEDBERG: *Arch. Int. Med.*, 1936, **58**, 620.
- Periarthritis Nodosa as a Demonstration of Hypersensitivity.** RICH and GREGORY: *Bull. Johns Hopkins Hosp.*, 1943, **72**, 65.
- Relation of Experimental Carditis to Rheumatic Fever.** McKEOWN: *J. Path. & Bact.*, 1947, **59**, 547.
- Relation of Hypertension to Ischemic Heart Disease.** HARRISON and WOOD: *Brit. Heart J.*, 1949, **11**, 205.
- Relation of Rheumatic Carditis to Subacute Bacterial Endocarditis.** MACILWAINE: *J. Path. & Bact.*, 1947, **59**, 557.
- Rheumatic Disease of Coronary Arteries.** GROSS, *et al.*: *Am. J. Path.*, 1935, **11**, 253. KARSNER and BAYLESS: *Am. Heart J.*, 1934, **9**, 557.
- Rheumatic Heart Disease.** CLAWSON: *Am. Heart J.*, 1940, **20**, 454. GROSS and EHRLICH: *Am. J. Path.*, 1934, **10**, 467, 488. GROSS and FRIEDBERG: *Am. J. Path.*, 1936, **12**, 855. KOLETSKY: *Am. J. Path.*, 1946, **22**, 351. LEARY: *Arch. Path.*, 1932, **13**, 1. SWIFT: *Medicine*, 1940, **19**, 417.
- Sarcoidosis of Myocardium.** YESNER and SILVER: *Am. Heart J.*, 1951, **41**, 777.
- Spontaneous Rupture of Heart.** BENSON, *et al.*: *Am. J. Path.*, 1933, **9**, 295.

- Subacute Bacterial Endocarditis.** GROSS AND FRIED: *Am. J. Path.*, 1937, **13**, 769.  
 HORDER: *Brit Med. J.*, 1920, **2**, 301. OKELL AND ELLIOTT: *Lancet*, 1935, **2**, 869.  
 WRIGHT: *J. Path. and Bact.*, 1925, **28**, 541.
- Subacute Myocarditis.** MAGNER: *Am. J. Med., Sci.*, 1939, **198**, 246. SAPHIR: *Am. Heart J.*, 1942, **24**, 167. SCHMIDT: *Am. J. Path.*, 1948, **24**, 97.
- Sudden Death.** WEISS: *New England J. Med.*, 1940, **223**, 793.
- Sulphonamide Myocarditis.** FRENCH AND WELLER: *Am. J. Path.*, 1942, **18**, 109.
- Syphilis of Heart.** COOMBS: *Quart. J. Med.*, 1932, **25**, 179. MARTLAND: *Am. Heart J.*, 1930, **6**, 1. MORITZ: *Arch. Path.*, 1931, **11**, 44. SAPHIR: *Arch. Path.*, 1932, **13**, 266.
- Trauma to the Heart.** BARBER: *Brit. M. J.*, 1940, **2**, 520; *Quart. J. Med.*, 1944, **13**, 137. SIGLER: *J. A. M. A.*, 1942, **119**, 855.
- Tumors of Heart.** BATCHELOR and MAUN: *Arch. Path.*, 1945, **39**, 67. GOLDSTEIN: *New York Med. J.*, 1922, **115**, 158. PRICHARD: *Arch. Path.*, 1951, **51**, 98.

## THE BLOODVESSELS

## THE ARTERIES

For the purposes of pathology it is convenient to divide the arteries into three classes: (1) The large or elastic type (aorta, carotid, etc.); (2) the medium or muscular type (radial, renal, superior mesenteric, etc.); (3) the intimate vasculature (small vessels such as the interlobular arteries and afferent arterioles of the kidneys). The distinction is useful, because each of these suffers from a different form of degenerative lesion; in the elastic type atheroma is the common lesion, in the muscular type the medial sclerosis of Mönckeberg, and in the intimate vasculature the diffuse hyperplastic type of sclerosis. Exceptions to this generalization will be encountered (*i.e.*, atheroma in small vessels such as the coronaries and cerebrals), but the generalization is useful nevertheless. Arterial lesions will be divided into three main groups for descriptive purposes: (1) Inflammatory lesions such as acute arteritis, syphilis, and rheumatism; (2) obliterating lesions such as thromboangiitis obliterans, periarteritis nodosa, and obliterating endarteritis; (3) the degenerative arteriosclerotic group, *i.e.*, atherosclerosis, Mönckeberg's medial sclerosis, and diffuse hyperplastic sclerosis. It must be remembered that the postmortem appearance does not necessarily represent the true condition of the artery during life. The small lumen and deeply folded intima and internal elastic lamina are due to contraction of the media after death, and will naturally vary with the amount of contraction. These artefacts are a fallacy which invalidates much of the work of measuring arterial walls and lumina.

## ACUTE ARTERITIS

**ACUTE PERIARTERITIS.**—Acute inflammation may attack an artery from the outside or the inside. An artery which passes through a focus of suppuration such as an abscess should be very liable to infection, but on the contrary it is quite resistant. Sometimes, however, the bacteria penetrate the wall and produce an acute arteritis and periarteritis, the media and adventitia being filled with polymorphonuclear leucocytes. The wall may be so weakened that hemorrhage may occur. Before the days of asepsis *secondary hemorrhage* was very common in operation wounds and was due to an acute suppurative arteritis produced by the septic ligature which was buried in the lacerated wall of the vessel. After a number of days the destruction of the wall was so great that hemorrhage occurred into the wound, and this was often fatal.

**ACUTE ENDARTERITIS.**—If an infected embolus from a septic thrombus in a vein or a vegetation of an acute endocarditis lodges in an artery it infects the vessel from within. Again the vessel wall becomes acutely inflamed. The results may be (1) septic thrombosis with breaking up of the thrombus and the formation of secondary metastatic abscesses; (2) the production, by weakening of the wall, of a small mycotic aneurism. This may burst and lead to severe or fatal hemorrhage.

## SYPHILIS OF THE ARTERIES

Syphilis attacks two important sets of vessels: (1) the aorta and its large branches, and (2) the cerebral arteries. Other vessels may be affected, but the clinical effects are of relatively little importance compared with these two.

**Syphilitic Aortitis.**—Aortitis is one of the commonest and most important of syphilitic lesions. It is usually found in males between the ages of thirty and fifty-five years. Symptoms seldom appear within five years of the primary lesion, although the aorta is probably infected from the very beginning of the disease. The spirochetes are lodged in the adventitia and media and are remarkably resistant to treatment, with the result that active lesions can almost always be found at autopsy, no matter how vigorous the treatment has been.

**SYMPTOMS.**—The chief symptom is substernal pain. With the progress of time an aortic aneurism may develop, a condition which will be considered later.

**LESIONS.**—The *gross appearance* is very characteristic unless it is obscured by the development of atheroma. The lesion begins in the aortic wall just distal to the aortic cusps, and spreads horizontally around the root of the aorta and distally as far as the mouths of the great vessels springing from the arch. This forms in many cases a zonal lesion picturesquely known as the girdle of Venus. Even more frequently the whole arch is diffusely involved. The probable reason why the suprasigmoid portion is the site of election is that it has such an abundant lymph supply, the spirochetes being carried in the perivascular lymphatics. The gross changes may be traced down as far as the diaphragm, where they suddenly stop, and as a rule the abdominal aorta is free from lesions.

In the affected area the intima is raised into patches, at first smooth and pearly, but later pitted and scarred. The intervening tissue is wrinkled like the bark of a tree. Longitudinal wrinkling is striking, but is not specific. It is the fine transverse wrinkling due to stellate scars which is highly characteristic of syphilis. The swelling of the intima may so narrow the openings of the coronary arteries that they are reduced to mere pin-points or one of them may be completely closed. In such a case there may be symptoms of coronary obstruction or the patient may suddenly drop dead. The disease does not spread along the coronary arteries. In a pure case the yellow fatty changes, calcification and ulceration of atheroma are absent, but it must be remembered that atheroma of the aorta often complicates syphilis. The adventitia is thickened, and the vessel is often unduly adherent to the mediastinum. When an attempt is made to strip off the adventitia it is found to be adherent, and the tear will take place through the middle of the media. The cut edge shows thickening of the intima with a corresponding thinning and interruption of the media. Owing to destruction of the elastic tissue by the spirochetes there is a dilatation of the vessel and especially of the aortic ring. In this way an extreme degree of aortic incompetence may be produced, for the cusps are quite unable to come together.

The condition of the *aortic valve* deserves close attention. In some cases the cusps are quite normal, even though there is a marked degree of incompetence. In other cases a characteristic condition of *syphilitic endocarditis* is present. This never occurs apart from syphilitic aortitis, and is never seen in the mitral valve. There are two distinctive lesions (Fig. 185): (1) the cusps are sclerosed and contracted, and the free edge shows a peculiar cord-like thickening quite unlike that seen in any other form of endocarditis. (2) There is a widening of the commissure, *i. e.*, a separation of the cusps at the point where normally they should meet, as if a wedge of tissue had been forced between each pair. The infection has evidently extended into the valve from the aortic wall, and the central part of the cusps is the least affected.



FIG. 185. -Syphilitic aortitis. The surface of the aorta is nodular, wrinkled, and scarred. There is widening of the commissure, and thickening of the free margin of the aortic cusps.

The *microscopic picture* is that of a periarteritis and mesaortitis with secondary changes in the intima. The earliest change is in the adventitia in the form of masses and linear streaks of lymphocytes and plasma cells (Fig. 186). These are collected around the vasa vasorum, owing to the distribution of the spirochetes in the perivascular lymphatics. The vasa vasorum normally penetrate only the outer third of the media but the spirochetes stimulate them to grow and branch so that they invade the whole thickness of the media. This is associated with fibroblastic proliferation and marked fibrous overgrowth of the intima which later becomes hyaline. The infection spreads into the media where there are foci of inflammatory cells, necrosis, and extensive destruction of the elastic tissue. It is the mesaortitis which is the most serious part of the disease, because with destruction of the elastic tissue the aorta loses its resiliency and either undergoes a general dilatation or develops an aneurism. New capillaries are formed which pass far into the media. The necrotic material is replaced

by scar tissue. It is the contraction of this scar tissue which gives rise to the characteristic wrinkling seen on the inner surface, so that the wrinkling is naturally a late phenomenon.

**RELATION OF SYMPTOMS TO LESIONS.**—The substernal pain is probably due to inflammation of the tissue at the root of the aorta. The destruction of elastic tissue and loss of elasticity may cause either general dilatation of the thoracic aorta as shown in the roentgen-ray picture, or the local dilatation known as an aneurism. Symptoms of coronary occlusion and even sudden death may be caused by closure of the openings of the coronary arteries by plaques of thickened intima. The three great dangers of syphilitic aortitis are: (1) aortic incompetence (the commonest), (2) stenosis of the coronaries, and (3) aneurism.

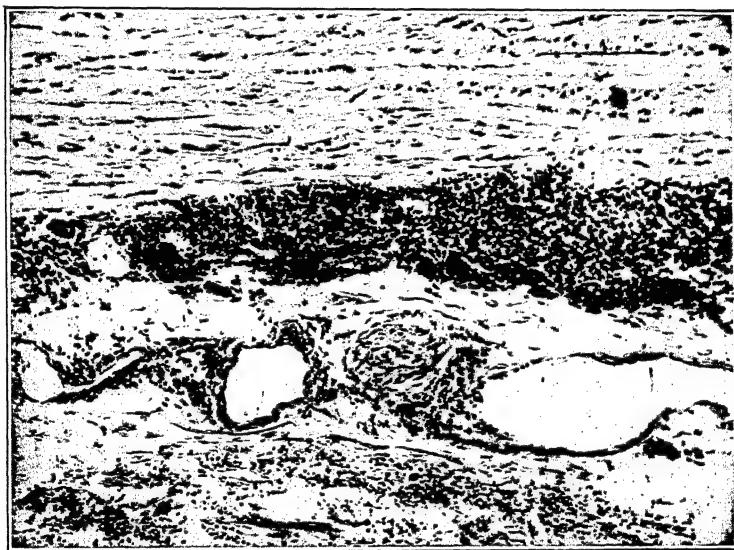


FIG. 186.—Syphilitic aortitis. A linear collection of inflammatory cells at the junction, of media and adventitia.  $\times 100$ .

**Syphilitic Arteritis.**—This is best seen in the central nervous system in the small arteries of the meninges and the vessels at the base of the brain. The lesion is both a periarteritis and an endarteritis (Fig. 187). As the spirochetes are in the lymphatics of the adventitia, the vessel is surrounded by a mantle of lymphocytes and plasma cells. There is some atrophy of the media, but this is not an important lesion. The intima shows a marked uniform thickening with great narrowing of the lumen, an endarteritis obliterans, quite different from the patchy atheroma which often affects these vessels. The narrowing of the lumen is apt to lead to thrombosis and cerebral softening. As the infection dies out the arteries become sclerosed and stiff, and have been likened to macaroni.

**RHEUMATIC AORTITIS.**—The lesion is similar to that produced by syphilis, but much less marked in degree. Definite rheumatic nodules (Aschoff bodies) may be formed in the adventitia, but usually there are merely collections of lymphocytes

and plasma cells around the vasa vasorum in the adventitia and to a lesser degree in the media together with a few large cells of the Aschoff type. The damage to the media is slight compared with that produced by syphilis and the lesion does not appear to be a factor in aneurism formation.

**RHEUMATIC ARTERITIS.** The visceral vessels may show very characteristic lesions first described by von Glahn and Pappenheimer. These lesions may occur in the arteries of the lung, kidney, pancreas, ovary and testicle. The lesion is a pan-arteritis, all the coats being involved (Fig. 188). The wall is filled with an inflammatory exudate containing much fibrin, so that it is much thickened. The

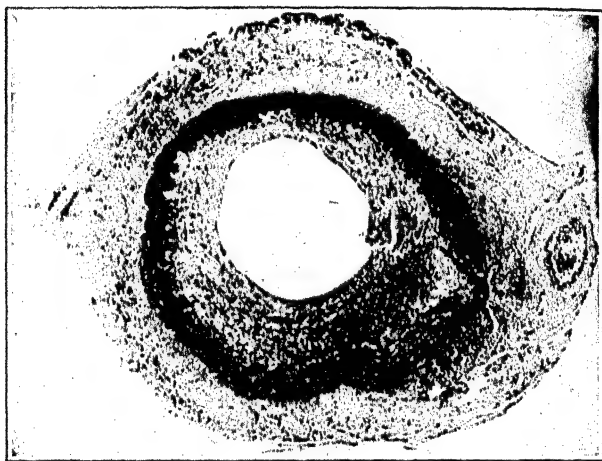


FIG. 187. Syphilitic endarteritis of basilar artery, showing uniform thickening of the inner coat and thickened internal elastic lamina (elastic tissue stain).



FIG. 188--Vascular lesion in rheumatic fever. Great thickening of the inner coat, and infiltration of all the coats by inflammatory cells.  $\times 200$ .



most remarkable feature is the subsequent vascularization of the damaged wall: new capillaries are formed in the wall so that the original lumen is surrounded by spongy vascular tissue. There is no thrombosis, so that the lesions do not injure the parts supplied by the vessels involved. In rheumatic fever the coronary arteries may show a severe exudative and necrotizing arteritis involving all the coats.

### THROMBO-ANGIITIS OBLITERANS

This remarkable condition is often called Buerger's disease, because it was Buerger who first recognized that the lesion was an inflammation of the wall with resulting thrombosis, and not a degenerative thickening of the intima allied to arteriosclerosis, as used to be thought. The symptoms are not due to the active disease but to the after-effects which develop in the chronic stage. The acute stage is rarely seen by the pathologist, so that he is apt to get a very erroneous and one-sided idea of the process.

The sex incidence is striking, for the disease is practically confined to men, although cases in women are now being reported. The race incidence, though also striking, is less extreme. In North America it is usually seen in young Russian and Polish Jews, but Gentiles may also suffer and even Scotsmen are not immune. It is a disease of young adult life. The lesions are usually in the vessels of the legs, but the arms may also be affected, sometimes exclusively.

The cause is unknown. Non-hemolytic streptococci have been found in the blood, and injection of these bacteria into sites adjacent to the femoral vessels has reproduced the disease in rabbits; a similar result is obtained by embedding segments of diseased human arteries alongside the femoral vessels (Horton and Dorsey). A surgeon who pricked his finger with a spicule of bone when amputating the leg in a case of Buerger's disease subsequently developed characteristic lesions in the digital arteries of the injured hand. The excessive use of tobacco especially cigarettes, has long been added by clinical observers to such factors as sex, race and age. The work of Sulzberger supports this idea. As a result of observations with the patch skin test he came to the conclusion that a large majority of patients suffering from this disease were hypersensitive to tobacco proteins, although not to nicotine itself. Allergic reactions may produce necrosis, and this may lead to aseptic inflammation. It has been suggested, though on rather insufficient evidence, that chronic typhus infection may play a part. It is probable that more than one exciting factor may be capable of producing the lesions in those who by race, sex and possibly heredity have predisposed vascular tissues.

**SYMPTOMS.**—In the acute stage there are usually no symptoms, but there may be red and painful spots which last about a week due to a migrating phlebitis in the superficial veins of the leg. The first symptoms are usually indefinite pains in one foot or cramp-like pains in the calf after walking a short distance, a condition known as intermittent claudication (*claudicare*, to limp). No pulse can be felt at the ankle. When the foot hangs down it becomes bright red (erythromelia) and throbs painfully. When the foot is raised it becomes more blanched than normally. Later in the disease trophic disturbances appear in the form of ulcers and gangrene of the feet. The formation of trophic ulcers is often accompanied by excruciating pain, and suicide is not an uncommon termination of this distressing disease.

**LESIONS.** The *acute lesions* are only likely to be seen if the superficial vessels are excised in the acute stage (migrating phlebitis). The media and adventitia are invaded by polymorphonuclear leucocytes and so is the perivascular tissue. Both arteries and veins are involved. There is an arteritis and periarteritis, a phlebitis and periphlebitis. Only a segment of the vessel is involved, but this segment may be short or long. Thrombosis occurs in the inflamed segment, with occlusion of the lumen. The clot may contain foci of polymorphonuclears or of endothelial cells and foreign body giant cells.



FIG. 189. —Thrombo-angiitis obliterans. The lumen is closed by fibrous tissue which is partially canalized. Hypertrophy of elastica. Elastic tissue stain.  $\times 40$ .

The *chronic lesions* are those seen when the leg is amputated for gangrene months or years later. All signs of active inflammation have disappeared, and artery, veins, and nerves are bound together in a dense mass of fibrous tissue. The clot has become organized and converted into fibrous tissue, and there is no sign of the original lumen (Fig. 189). New vascular channels lined by endothelium are formed in the fibrous mass, so that the lesion is often mistaken for a mere thickening of the intima, an endarteritis obliterans. Thickening of the elastic tissue, both internal and external is a striking feature. There is no calcification, so that the vessel throws no shadow in the roentgen-ray picture.

**RELATION OF SYMPTOMS TO LESIONS.**—The symptoms are due to loss of the peripheral blood supply or to disturbances of the collateral circulation which is set up. The prognosis depends on the extent to which the collateral circulation can be established, and modern methods of treatment are directed to the encouragement

of this circulation. The cramp-like pains in the muscles are due to the painful spasm which accompanies an insufficient blood supply when the muscle is in a state of activity. The flushing of the foot when it hangs down and its blanching when elevated is due to loss of vasomotor control, the nerves in the periadventitial tissue being involved in the inflammatory and sclerotic process. The trophic lesions may be due to a similar cause, a view supported by the fact that when the affected segment of vessel is resected the trophic lesions may heal quickly and permanently (Leriche).

**Periarteritis Nodosa.**—This disease belongs to a group of necrotizing inflammations of arteries, which includes temporal arteritis, disseminated lupus erythematosus, and possibly other conditions. They in turn belong to the larger group of the collagen diseases. Fibrinoid necrosis, allergic inflammation, thrombosis with resultant ischemic lesions, and wide distribution are the outstanding features. The lesions of periarteritis nodosa affect the visceral rather than the peripheral vessels as in thrombo-angiitis obliterans. The cause is unknown, but it is not unlikely that the disease represents an anaphylactic type of hypersensitivity. The very widespread character of the lesions is in favor of this idea, and also the fact that periarteritic lesions have been found in a number of cases of serum sickness and hypersensitiveness to sulphonamides. Rich has reported a series of such cases, and has succeeded in producing diffuse periarteritis nodosa experimentally by establishing in rabbits a condition analogous to serum sickness in man.

**SYMPTOMS.**—The disease usually runs an acute febrile course, often ending fatally in a few weeks. As the lesions are so varied and widespread the clinical picture may be equally varied, but there is a certain recognizable clinical pattern, the outstanding features being prolonged fever, weakness, quick pulse, limb pains suggesting rheumatism or neuritis, chest symptoms such as cardiac pain or asthma, abdominal pain, and finally albuminuria and hematuria, often associated with hypertension. Blood examination reveals a constant leucocytosis, eosinophilia in about one-fifth of the cases, a high sedimentation rate, and a negative blood culture. This complex symptomatology, corresponding to no system disease, may itself suggest a correct diagnosis.

**LESIONS.**—The principal vessels affected are those of the gastro-intestinal tract (mesenteric and celiac axis), the kidney and the heart, but the brain, lungs and skin may also be involved. The name is misleading, for the lesion is a panarteritis rather than a periarteritis, and in my experience most of the cases fail to show the "nodosa" feature. This term indicates the presence of small inflammatory nodules scattered along the artery like peas in a pod. There may be hundreds of these nodules on the mesenteric vessels. The fundamental *microscopic* change is increased permeability of the vessel wall (Pagel). The earliest change is edema and escape of fibrinogen into the wall with the formation of fibrin or material which stains like fibrin. This is followed by fibrinoid necrosis first of the media and later of the other coats. Fragmentation of the elastica is a prominent feature which explains the frequency of aneurism formation. Inflammatory cell infiltration involves all the coats (Fig. 190.) At first the cells are neutrophils and eosinophils; later these are replaced by more chronic types. Owing to

involvement of the intima thrombosis is common, and small infarcts are produced in the heart, kidneys and other organs. Renal lesions are particularly common, occurring in 75 to 85 per cent of the cases (Davson *et al.*). In addition to multiple infarcts there may be diffuse changes in the renal parenchyma resembling those of glomerulonephritis. Hypertension may be associated with healed occlusive lesions of the branches of the renal artery.

The disease usually runs a rapidly fatal course, but it may be of more subacute type, ending up as *healed periarteritis nodosa*. This produces a clinical picture of great complexity based on multiple chronic ischemic lesions. Autopsy may reveal contracted kidneys, coronary occlusion,

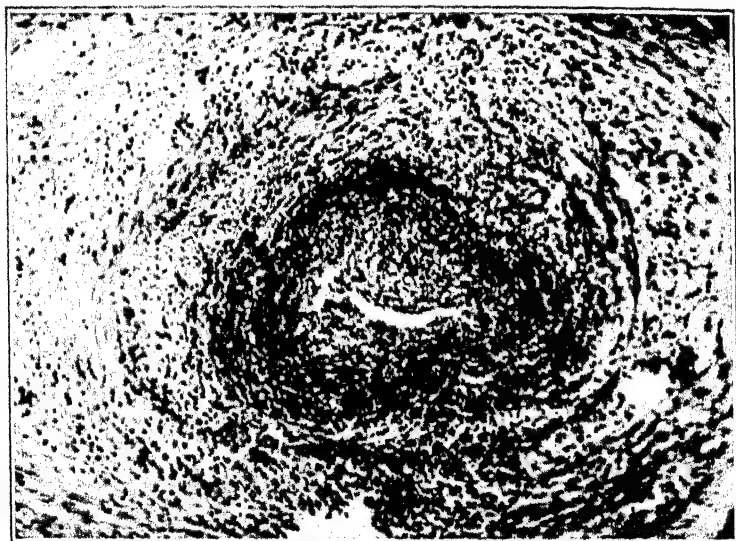


FIG. 190.—Periarteritis nodosa. All the coats of the vessel are infiltrated by inflammatory cells.  $\times 80$ .

myocardial scars, *hepar lobatum*, atrophy of adrenals and pancreas, etc. The use of cortisone has been followed by apparently complete healing of all the lesions in the course of a few weeks. Unfortunately healing is accompanied by fibrous occlusion of the arterial lumen and the production of multiple infarcts.

There may be acute abdominal symptoms due to involvement of the mesenteric arteries, acute cardiac symptoms from coronary artery involvement, muscular pains simulating myositis or trichinosis, etc. Neuritic pains are common; they are due to lesions of the peripheral nerves (Kernohan and Woltman). Death is often due to a ruptured aneurism. In the healed stage the symptoms will be those of ischemic sclerotic lesions of the heart, kidneys, etc.

**TEMPORAL ARTERITIS.**—This condition, first described by Horton, Magath and Brown in 1932, is a chronic inflammatory process involving the temporal arteries of elderly persons, but extending to the arteries of the scalp and face. The vessels can be felt as cord-like swellings. Cooke and his associates have shown that,

whilst the name is conveniently descriptive, the lesions are by no means confined to the temporal arteries, and may involve also the aorta, radial, subclavian, femoral, coronary, renal, mesenteric, and retinal arteries. The inflammation appears to spread from the adventitia to the media. There is marked thickening of the intima due to the formation of a zone of loose cellular connective tissue. The walls of the involved vessels (the medium-sized muscular arteries) are thickened and thrombosis may occur. Foreign body giant cells formed in response to disintegration of the elastica is a striking feature of many cases. For this reason the name giant-cell arteritis has been suggested instead of the misleading temporal arteritis which has become a misnomer (Gilmour). Unfortunately giant cells occur in other destructive lesions of arteries such as Buerger's disease. Eosinophils are sometimes present in considerable number.

The onset of the illness is marked by malaise, myalgia and arthralgia, anorexia, and loss of weight. After some months more localized symptoms appear, especially severe headache, mental confusion, and visual disturbance which may end in blindness. There may be symptoms suggesting generalized arterial disease. A variable degree of fever is often present. The disease is self-limited, but owing to its generalized nature it may end fatally.

The etiology is unknown. It will be seen that the condition bears a close resemblance to such generalized arterial diseases as periarteritis nodosa and Buerger's disease, in both of which the inflammation may be allergic in character. It occurs at an older age period than these diseases.

**Disseminated Lupus Erythematosus.**—Lupus erythematosus is a disease which may occur in two very different forms, the one chronic, benign, involving both sexes equally, and characterized by a butterfly pattern of discoid lesions of the skin of the bridge of the nose and cheeks, the other an acute and fatal disease predominantly in young women, with lesions disseminated in various organs and tissues including the skin. At first sight the two conditions appear to be distinct and unrelated, but occasionally, especially in women, there may be a transition from the chronic localized to the acute disseminated form.

Disseminated lupus is most likely to occur in young women, especially in those with red hair, a tendency to freckling and an inability to tan. As these peculiarities of pigmentation are believed to be under hormonal control, either pituitary or adrenal, it is possible that the target tissues may be conditioned by endocrine influence so that they react violently to the unknown etiological agent. This reaction seems to be allergic in character.

The clinical manifestations are extremely variable. The onset may be abrupt and the course short and stormy ending fatally in six or eight weeks, or the progress may be slow and insidious over a number of years with remissions and exacerbations. Although the butterfly erythematous patch across the bridge of the nose is a characteristic feature, skin lesions may be absent. Fever, leucopenia, and enlargement of spleen and lymph nodes are common. Hyperglobulinemia is a constant feature. The patient presents a toxic appearance, and frequently looks more ill than the clinical data seem to justify. The plasma contains a factor which when mixed with normal bone marrow causes the formation of (a) rosettes or clumps of leucocytes and (b) a characteristic inclusion-containing cell, the *L.E.* or *lupus erythematosus cell* (Fig. 191). The *L.E.* phenomenon is believed to consist of lysis of leucocytic nuclei followed by phagocytosis of the lysed

material by polymorphonuclears. The factor is a lytic factor, apparently an antigenic fraction of serum gamma globulin. The phenomenon appears to be related to the presence of blood platelets which release antigenic protein on disintegration, because it is enhanced by blood coagulation (Zimmer). The L.E. cells must not be confused with erythrophagocytosis nor with tart cells, the latter being monocytes which have ingested a lymphocytic nucleus. The factor disappears in remissions and reappears during relapses. The L.E. cell, first described by Hargraves in 1948, has become a feature of great diagnostic value in the disease, but it must be realized that the test is really a test for abnormal globulins in the blood. The inclusion material is homogeneous and basophilic. It gives a positive Feulgen reaction, suggesting that it is nuclear in origin. The basophilic material may be extracellular.

Klemperer has called attention to hematoxylin-stained bodies, first described by Libman and Sacks in 1924 and again by Gross in 1932. The

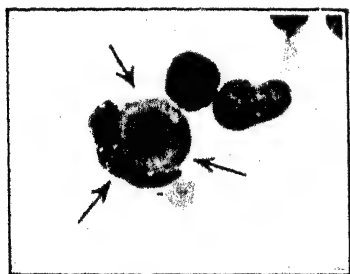


FIG. 194. -- L. E. cell. (Kindness of Dr. A. J. Blanchard.)



FIG. 191A. -- Wire loop lesions in disseminated lupus.

*hematoxylin bodies* are believed to be pathognomonic of disseminated lupus. They form large aggregates in the endocardial vegetations and lymph nodes, and smaller collections and single free bodies in the glomeruli, in the walls of vessels in many organs (especially the ovary), and in connective tissue. The hematoxylin bodies contain depolymerized desoxyribonucleic acid, so that they may represent a disturbance of nucleoprotein metabolism. It is possible that free nucleoproteins in various stages of decomposition may be circulating in the blood, and that as these are foreign to the normal blood proteins they represent the antigenic factor responsible for the L.E. phenomenon. Both the L.E. cells and the hematoxylin bodies give the same reactions with the Feulgen reagent and with methyl green. The hyaline thrombi in the glomerular capillaries and the wire loop lesions may have a similar origin.

The lesions are widespread in many organs, and are particularly marked in the vessels, in these respects resembling periarteritis nodosa. Although a classical case of disseminated lupus differs greatly from a classical case of

periarteritis nodosa it is doubtful if the distinction is fundamental. I have encountered a number of instances where the features and lesions of the two diseases were combined. In general the lesions of lupus tend to be more degenerative (necrotic) and those of periarteritis more inflammatory in type, but combinations occur. In periarteritis the medium-sized vessels (coronary, mesenteric) are affected, in lupus the small arteries and arterioles and even the capillaries. Perhaps the most important difference is in sex, periarteritis being predominantly a male disease, and lupus largely though not exclusively female. Sex may be a conditioning factor which determines the target organ and the character of the lesions. The basic lesion is a widespread fibrinoid degeneration of collagen and ground substance, to which may be added a minor degree of reactive inflammation. One of the striking effects of the involvement of the capillaries is an increased permeability, which is seen particularly in the skin. As disseminated lupus is one of the collagen diseases, it is natural that arthritis may be a feature. Heavy deposits of fibrin are found on the synovial membrane of the affected joints.

For descriptive purposes the principal lesions are cardiac, renal, vascular, and cutaneous. In the *heart* (in less than half the cases) the striking gross lesion may be the flat warty vegetations described by Libman and Sacks in 1923 extending on to the mural endocardium. Microscopically the basic lesion is fibrinoid degeneration of the connective tissue of the endocardium, myocardium and pericardium. In the *kidney* the characteristic microscopic lesions are in the glomerular tufts: (1) the so-called "wire loop capillaries," (2) focal necrosis of the tuft. The wire loop appearance is due to thickening of the basement membrane of the capillaries giving a resemblance to bent wire similar to that of early amyloidosis (Fig. 191A). With haematoxylin and eosin the wire loop appearance seems to be due to a thickening of the basement membrane of the capillaries giving a resemblance to bent wire. With finer differential staining, however, and also with phase microscopy the wire loop material is seen to be deposited between the epithelial and the endothelial basement membranes (Churg and Grishman). An appearance suggesting hyaline thrombi in the capillaries is probably due to protrusion into the lumen of the fibrinoid material in the vessel wall; true thrombosis is rare. In the *spleen* the small arteries show a periarterial fibrosis, swollen bands of collagen giving a characteristic "onion-skin" type of lesion. Teilum suggests that the periarterial lesions in the spleen, the wire-loop lesions in the kidney, and other manifestations of the disease are the result of allergic alterations (paraamyloidosis) associated with the hyperglobulinemia. The *vascular* lesions are most common and severe in the kidneys, but they may be present in any organ in the body. In advanced cases there may be complete fibrinoid necrosis of all the coats of the arterioles. Marked thickening of the intima may cause great narrowing of the lumen. A fulminating necrosis may call forth an inflammatory cellular reaction (lymphocytes, plasma cells, a few polymorphonuclears). In the *skin* fibrinoid degeneration occurs in the upper layer of the corium involving both collagenous fibers and ground substance. The arterioles and capillaries show the usual changes. In conclusion it may be said that disseminated lupus is a disease with disseminated lesions of the minute blood

vessels with a tendency to secondary thrombosis. It is often associated with inflammation and proliferation of the serous membranes, including the endocardium, and with thrombopenia. Leucocytosis is characteristic of periarteritis, just as leucopenia is characteristic of disseminated lupus.

**DIFFUSE COLLAGEN DISEASE.** In 1933 Klinge pointed out that in rheumatic fever and rheumatoid arthritis the basic change was in the intercellular components of the connective tissue. This change consisted of fibrinoid degeneration of the collagen and myxomatous swelling of the ground substance. As similar changes occurred in experimental hypersensitivity he concluded that they were allergic in nature. Fibrinoid necrosis, however, is observed in the base of peptic ulcers, in pancreatic necrosis, in experimental hypertension, and in arteries following injection of adrenalin. Klemperer points out that "an apparent similarity in the histologic picture does not denote identity of tissue lesions and certainly not unity of processes and pathogenesis." And yet it would seem that there should be a common denominator for the changes in the intercellular tissue in various diseases. Fibrinoid degeneration with cellular exudate is the factor common not only to rheumatic fever and rheumatoid arthritis, but also to periarteritis nodosa, disseminated lupus, dermatomyositis and scleroderma. These conditions have, therefore, been included under the blanket term of the collagen diseases. The term fibrinoid degeneration was introduced in 1880 by Neumann to indicate a change in collagen fibers which assume some of the staining and structural qualities of fibrin. Other workers believe that it represents a change in the physical nature of the ground substance or that it actually is fibrin, formed from an exudate of fibrinogen. Glynn and Loevi find that fibrinoid differs from fibrin in its fibrillar structure as revealed by silver impregnation and by tryptic digestion, and believe that it is produced by the impregnation of collagen fibers with a material containing polysaccharide. This is responsible for the intensely positive reaction with the McManus PAS (periodic acid-Schiff) stain. It would appear that the fundamental lesion is an alteration in the physical character (depolymerization) of the mucopolysaccharides of the ground substance with secondary changes in the fibers.

Collagen disease is not a disease entity "in spite of the impatience of clinical investigators and a peculiar worship of diagnostic terms which has led to an exaggerated popularity of the diagnosis collagen disease. There is a danger that it may become a catch-all term for maladies with puzzling clinical and anatomical features" (Klemperer). We have already seen that there are distinct variations and differences between the various members of the group with their different target organs. "These differences, together with differences in the anatomical distribution of the lesions, permit the recognition of distinct disease entities on pathological as well as on clinical grounds. The same theme runs through all of them, but the variations on the theme are distinctive for each disease" (Duff).

**ENDARTERITIS OBLITERANS.** This is not a separate entity due to a single cause, but a group of conditions in which the chief feature is a thickening of the intima with narrowing or even obliteration of the lumen. The change may be physiological, as in closure of the hypogastric vessels and the ductus arteriosus. It is seen in the involution of old age, especially in the female reproductive organs when they have ceased to function (uterus, ovaries, breast). In organizing granulation tissue the vessels are closed by the same process. A marked degree of obliterating endarteritis is seen in the neighborhood of many chronic inflammatory foci, *e.g.*, gastric ulcer. In syphilis of the small arteries endarteritis is one of the chief features. In all of these cases the thickening is due to a proliferation of the subendothelial connective tissue.

**AYERZA'S DISEASE.** This is a form of endarteritis obliterans affecting the smaller branches of the pulmonary artery. The patients were called "black cardiacs" by



Ayerza because of the very marked cyanosis. The chief symptoms are dyspnea, chronic cyanosis, and compensatory erythrocytosis (polycythemia). The red cells may number 10,000,000. Owing to the increased resistance in the pulmonary circulation the right side of the heart is much enlarged.

The essential lesion is a pulmonary endarteritis. The main branches of the artery are dilated and sclerosed, but the chief change is in the small arteries and arterioles. These show an endarteritis obliterans, with marked thickening of the intima and great narrowing of the lumen. Thrombosis is common. It would perhaps be better to regard the condition as a syndrome rather than a disease entity with a single cause. The introduction of fibrin thrombi and other foreign material into the pulmonary circulation of the experimental animal results in pulmonary endarteritis, and I have seen the same thing happen in a patient in whom small thrombotic emboli from a localized dilatation of the left innominate vein plugged countless numbers of pulmonary arterioles with resultant extreme pulmonary hypertension.

### ARTERIOSCLEROSIS

The term arteriosclerosis is used in different senses by different writers. To the majority it is synonymous with atherosclerosis, although the standard medical dictionaries do not recognize this identity; to a few it means the diffuse sclerotic form of arterial disease; and to still others, with whom I agree, it signifies an omnibus term which includes a variety of conditions not necessarily related to one another. It seems better for the present to use arteriosclerosis in a broad sense to include a variety of non-inflammatory forms of arterial disease which may or may not have a common etiology.

Three main forms may be distinguished, which differ sharply in microscopic appearance and in some degree in distribution. These are: (1) atherosclerosis, a patchy lipoidal degeneration of the intima, by far the commonest and most important of the three; (2) medial calcification, commonly called Mönckeberg's degeneration; and (3) diffuse arteriolar sclerosis, a degenerative thickening of the intima of the smaller visceral arteries which may assume more than one form. Medial fibrosis of the medium-sized arteries is common in persons over middle age. Collagenous thickening of the intima (endarteritis obliterans) may cause so marked a narrowing of the lumen of the smaller arteries of the extremities in the later period of life as to lead to gangrene.

1. **Atherosclerosis.**—Atherosclerosis or atheroma is a nodular type of arteriosclerosis which affects the large arteries, especially the aorta, and the small arteries, particularly the coronaries and cerebrals. It is the fact that these arteries supply the myocardium and the brain, and that this is the only form of arteriosclerosis which commonly predisposes to thrombosis, which lends to atheroma a sinister significance. The medium-sized arteries of the muscular type are not so liable to the disease.

**Lesions.**—The *gross appearance* is most readily studied in the aorta. The most severe changes are seen in the abdominal aorta, especially in elderly persons; they are more marked in the descending than the ascending thoracic aorta. Thus the distribution of the lesions is the reverse of that seen in syphilis. They are especially marked around the mouths of the intercostal and lumbar arteries. The earliest change takes the form of

yellow streaks in the intima representing deposits of fat. Such fatty streaks may be seen in young people after an attack of one of the infectious fevers. In such persons it seems probable that the lipid deposits may be absorbed and that the lesions may never progress to true atheroma, so that a distinction may be drawn between the atheromatosis of youth and the

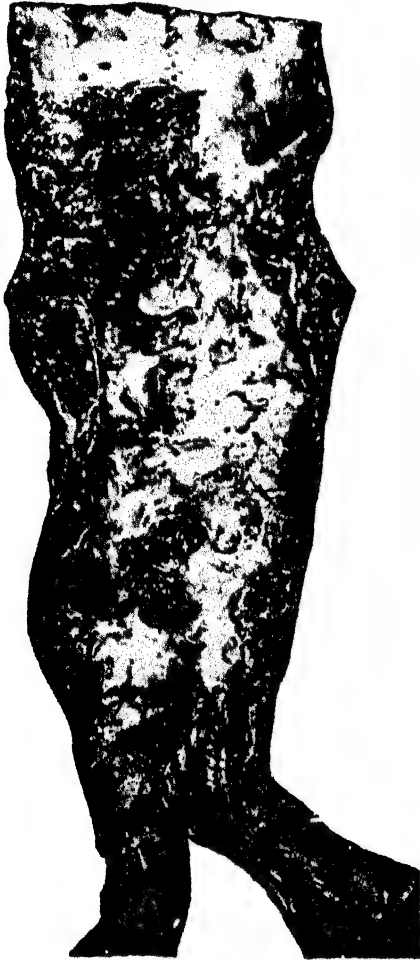


FIG. 192.—Atheroma of abdominal aorta. Thickened patches surround the openings of the lumbar arteries and there is much ulceration. (From Boyd's Surgical Pathology.)

atherosclerosis of advancing years. The intima over the fatty patch becomes raised and at the same time thickened, so that the yellow color of the underlying material is no longer visible and the plaque becomes pearly and looks as if a drop of wax had fallen on the lining of the aorta. The patch contains a soft, yellow, porridge-like material from which the disease takes its name (*athero*, gruel). The process of atheromatous softening may reach the surface, and the pultaceous material is then discharged into the lumen of the vessel and an atheromatous ulcer is formed (Fig. 192). A thrombus may be formed on the surface of the ulcer which sometimes is the starting-point of an embolus. Calcification of the lesion is very common, since lime salts are readily deposited in fatty material, and in advanced cases the wall of the aorta is converted into a calcareous tube which is cracked in places as readily as a shell. Blood may penetrate through these cracks and separate the layers of the wall. The more advanced the age of the patient, the more likely is there to be marked calcification, especially in the lower part of the abdominal aorta. To sum up, the main features are: (1) fatty streaks, (2) wax-like plaques of heaped-up intima, (3) atheromatous ulcers, and (4) calcification.

In the small arteries such as the coronaries and cerebrals the chief characteristic of the lesions is their patchiness. Yellow nodules are seen both on the outer and inner surfaces of the arteries in the circle of Willis, etc. In these small vessels the nodules may cause serious narrowing or even complete occlusion of the lumen. This, for instance, is the chief cause of gradual coronary artery occlusion. The aorta is so wide that the nodules can have no appreciable effect on its lumen.

The chief *microscopic lesion* is in the intima. There is first a deposit of lipids, chiefly cholesterol ester, in the deepest part of the intima. Some of the lipid is taken up by macrophages, which become pale, swollen, vacuolated "lipid cells." The change gradually extends from the deeper part of the intima to the surface. At the same time there is a thickening of the connective tissue of the intima overlying the fatty area, *i. e.*, the sclerotic part of the atherosclerotic process. Cholesterol, like silica, may remain as an inert substance in the tissues and act as a chronic stimulant to fibroblasts. This new tissue becomes hyaline so that no cells can be seen in it. The deeper part of the lesion consists of a kind of pulp in which the cholesterol ester is broken up into crystals of cholesterol which appear in paraffin sections as needle-like clefts. In frozen sections the lipid can be stained with Sudan and other stains for fat. Calcium salts are deposited in the fatty material and appear as fine granules stained dark blue with hematoxylin. The same change is seen in the small arteries, but here the internal elastic lamina tends to be broken up into strands, some of which pass superficial and some deep to the lesion, uniting on the far side.

*Intimal hemorrhage* is a common feature of atherosclerosis. Paterson first drew attention to it in the coronary arteries, and it has been found in the pulmonary, cerebral, carotid, renal and femoral arteries. The hemorrhages, which are more frequent in hypertension, are often multiple, and that they may occur at intervals is indicated by the presence of old hemosiderin in the atheromatous lesions. The hemorrhage seems to be from intimal capillaries which develop in atherosclerosis and communicate with the lumen of the artery. These capillaries are illustrated in Fig. 175, page 325. The hemorrhage enlarges the atheromatous plaque, and may narrow or occlude the lumen of a small vessel such as a coronary or a cerebral artery. In a large artery such as the femoral this effect is negligible. The intimal hemorrhage may further add to and intensify the atherosclerotic process. Finally, it may rupture into the lumen of the artery and initiate thrombosis. Willis, who found intimal hemorrhage in the femoral and popliteal vessels in 55 cases in 152 routine autopsies, draws an interesting analogy between atherosclerosis and scurvy. In both of these the fundamental fault is in the ground substance of the vessels, new capillaries are formed, hemorrhage is common and thrombosis may be an accompaniment. Moreover in scorbutic guinea pigs Willis observed an abundant deposition of lipids in the ground substance of the aorta in from 2 to 3 weeks.

Hartroft has demonstrated in all the atheromatous aortas he has examined the presence of a yellowish-brown pigment apparently identical with the *ceroid* found in the cirrhotic livers of choline-deficient rats. The striking feature of this substance is that it gives an intense staining with the Sudan stains for fat in paraffin sections, and yet is insoluble in alcohol, xylol and other fat solvents. It appears to be derived, at least in part, from red blood cells.

It used to be thought that degenerative changes in the media were primary, and those in the intima merely secondary (Thoma). This view, for long out of fashion, is beginning again to attract attention. Blumenthal and his associates have shown by means of micro-incineration that the bluish granular material which is so familiar a feature in the media of the

aorta in old persons is calcium. They found, moreover, that micro-incineration was a more sensitive indicator of calcium than staining with hematoxylin. The calcium appears to be deposited in the elastic fibers, so that calcification is proportional to loss of elasticity. Indeed the primary change seems to be a degeneration of the elastic fibers with the formation of elastic fragments and granules. Elastic degeneration is one of the basic age changes, not only in the arteries but in other tissues such as skin. The distribution of calcification varies in different arteries, corresponding with variation in the distribution of elastic tissue. Syphilitic aortitis, in which the elastic fibers are destroyed, is not associated with medial calcification. Such calcification appears to precede the formation of atheromatous plaques in the intima, and it occurs more frequently than do the plaques.



FIG. 193. Atheroma of a cerebral vessel. The thickened intima shows degeneration in its deeper layers, and there is some atrophy of the media underlying the thickened plaque.  $\times 125$ .

The media may show some atrophy deep to the intimal plaque. In the aorta this is slight, but in the small vessels it may be extreme in degree, because the blood-pressure forces the intimal plaque outward producing secondary atrophy of the media.

**EFFECT ON THE VESSELS.**—The elasticity of the aorta is impaired and it becomes widened, particularly in old people. At the same time it is elongated, so that it pursues a tortuous course. There is none of the extreme destruction of the media and adventitia seen in syphilis, so that aneurism is a rare sequel, but it may occur. In the small vessels there may be great narrowing of the lumen (Fig. 193) with softening of the brain and necrosis and scarring of the myocardium. An atheromatous patch on a cerebral vessel is a source of weakness, and is a very common cause of cerebral hemorrhage, and also of cerebral thrombosis. It may lead to the formation of a small aneurism owing to involvement of the internal elastic lamina by the atheromatous process.

**ETIOLOGY.**—Atherosclerosis is responsible for about 95 per cent of deaths from coronary disease, about 50 per cent of deaths from diabetes, and about 50 per cent of those from cerebrovascular disease. The etiology of the condition is therefore of prime importance if anything is to be done to prevent this common and crippling disability of declining years, but in spite of a vast amount of experimental work that has been and is being done, the problem remains unsolved.

It is probably a mistake to assume that there must be any one single and sufficient cause of atheroma. Inflammatory adventitial lesions such as those of rheumatic fever may be associated with intimal changes indistinguishable from arteriosclerosis. This is best seen in the coronary arteries of young people (Saphir and Gore). After hemorrhage into the intima the unabsorbed red cells form a mass in which cholesterol crystals are precipitated and which may be identical with atheromatous material. In 1852 Rokitansky suggested his encrustation hypothesis in which atheroma was traced to organization of a thrombus which became incorporated with the intima with vascularization from the adventitia and the intima, hemorrhage from the new vessels which lack a good collateral circulation, and liberation of cholesterol from the erythrocytes. This theory has been revived by Duguid, more particularly with regard to coronary atheroma, but including also atheroma of the aorta. Duguid's concept supported by Crawford and Levene and well reviewed by McLetchie, may explain the development of atheromatous lesions in some cases. If it is correct, however, it is difficult to explain the absence of atheroma in veins where thrombosis followed by vascularization is so common. There are different routes by which a goal may be reached.

Four years after Rokitansky's paper Virchow, his arch opponent, introduced the concept that atheroma is due to an imbibition of plasma by damaged intima with consequent deposition of lipid in the ground substance. This concept is not as simple as might at first appear, for it leaves unanswered the following questions: Does the intimal degeneration precede or follow the imbibition of plasma? Is a heightened blood lipid level a predisposing or perhaps a necessary factor? Does increased permeability of the endothelium due to infections, etc. allow the plasma to enter the intima? What part do accessory factors such as strain, hypertension and age play?

In trying to form for ourselves a concept of the pathogenesis of atheroma it is well to distinguish between the parts played by ground substance, elastic tissue, fibrous tissue and lipid. The most fundamental of these may be the ground substance, the matrix from which elastic and fibrous tissue may be formed and to which they may return. It is, moreover, a prime factor in controlling tissue permeability. It consists mainly of the mucopolysaccharides hyaluronic acid and chondroitin sulphate, the latter being the sulphated form of the former. It stains metachromatically with toluidin blue and is beautifully demonstrated by the colloidal iron technic which stains it an intense blue, especially when it is increased in amount or altered in character as the result of disease (Rhinehart and Abul-Haj). My colleague H. E. Taylor has shown that in infancy the metachromatic substance is distributed evenly throughout the entire width of the wall of the aorta between the elastic fibers, but with advancing years the ground

substance becomes condensed in focal masses of foamy metachromatic material especially in areas showing fragmentation of elastic fibers. It may be that there is a relationship between increased metachromia and degeneration of the elastica, the highly polymerized mucopolysaccharides of elastic tissue being returned to the metachromatic pool. The process is seen in most striking form in medionecrosis of the aorta, and is not necessarily associated with atheromatous plaques. This medial degeneration is met with at all ages, but is most pronounced in later years and in cases of arterial hypertension. Destruction of the elastica may be due to overactivity of the enzyme elastase or to lack of the inhibitor of the enzyme which is present in normal serum. Vitamin deficiency might play a part in such activation, as suggested by the increase of metachromatic mucopolysaccharides in the intima and media of the coronary arteries in pyridoxine deficient monkeys (Rinehart and Greenburg).

Diffuse intimal fibrosis is also observed both in early childhood and in the apparently normal adult aorta (Wilens). Some of this fibrosis may be not truly intimal but may also involve the media. What at first sight appears to be markedly thickened intima may prove on more careful examination to be thickened intima plus degenerated and fibrosed media in which all the elastic tissue has been lost. Although intimal fibrosis is not necessarily associated with deposits of lipids it may be an integral part of the atherosclerotic process.

The lipid, cholesterol, is the most contentious of the four elements under discussion. It is the one most evident both to the naked eye and on microscopic examination, especially when fat stains are used on frozen sections. The baffling question still remains as to whether its presence is merely the result of increased permeability of tissue brought about by change in the character of the ground substance or whether the lipid deposits are the *fons et origo* of the whole process.

Leary, in a paper summing up the work of many years, says that the relation of crystalline ester cholesterol to the lesions is as specific as is that of the tubercle bacillus to tuberculosis. But we must remember that tuberculoid reactions may be produced by a variety of agents. Atheroma is almost exclusively a human disease among mammals, although it may occur naturally in birds. This fact discounts to a marked degree much of the experimental work on animals. It was Anitschkow who first produced atheromatous deposits in the aorta of rabbits by feeding them a diet rich in cholesterol. Leary and others have confirmed these results in the coronary arteries as well as in the aorta. Duff, in an excellent review, points out that the results of cholesterol feeding in rabbits affords no grounds for the belief that human atherosclerosis is related to high cholesterol in the diet or to hypercholesterolemia. The normal blood cholesterol of the rabbit is low and is markedly raised by the administration of cholesterol, whereas in man the normal level is high.

It would appear that the size and physical state of the lipid molecules may be more important than the level of serum lipid. Gofman and his associates have shown by measuring the flotation rate in the ultracentrifuge that several species of lipoproteins may exist in the human subject. The units used are called Svedberg flotation or S<sub>f</sub> units. Two classes of lipoproteins are elevated significantly in pa-

tients with coronary artery disease, namely those between S<sub>f</sub> 12 and S<sub>f</sub> 20 (the S<sub>f</sub> 12-20 class) and those between S<sub>f</sub> 20 and S<sub>f</sub> 100 (the S<sub>f</sub> 20-100 class). As these two classes represent only 10 to 15 per cent of the total lipids of serum, it would seem that 85 to 90 per cent of serum lipoproteins are not related to atherosclerosis, so that estimations of total serum cholesterol are without value and indeed misleading. It is believed that the S<sub>f</sub> 10-20 molecules bear a significant relationship to human atheroma, and that these macromolecules (giant molecules) may become entrapped between the overlying endothelium and the underlying elastica. When the neutral fats and fatty acids are absorbed the cholesterol and its esters are left behind. The significant S<sub>f</sub> levels are raised in certain diseases, *e.g.*, diabetes, nephrosis, myxedema, hepatitis and xanthomatosis. The level is also raised in obesity, and it is not without interest to note that atheroma is ten times more common in the obese than in the lean. The administration of heparin has a remarkable influence in shifting the serum lipoprotein pattern toward normal.

In addition to the level of blood lipids, consideration must be given to the enzyme systems in the vessel wall which deal with the lipids. These may be different in different species and this difference may explain why the dog and cat are so resistant to dietary atheroma which is so readily produced in the rabbit. When the dog's aorta is rendered ischemic by cauterization, atheromatous lesions develop in the ischemic areas when the animal is fed cholesterol. If the enzyme system is inadequate to deal with the lipids presented to it the latter cannot fail to accumulate in the intima.

In this connection reference must be made to the rat, an animal in which it is practically impossible to raise the level of blood lipids or to produce atherosclerosis by feeding cholesterol alone. The reason for the immunity of this species has been the subject of much speculation. An interesting explanation has been recently suggested by my colleague Dr. P. Constantiniides who, in confirmation of much earlier claims, found that the connective tissue of the rat is abundantly supplied with mast cells, whereas in the atherosclerotic susceptible rabbit these cells are practically absent. The mast cell is considered to produce heparin in the body, and the injection of this substance, which is related chemically to mucopolysaccharides, inhibits lipemia and retards atherogenesis in the cholesterol fed rabbit. It may be, therefore, that the presence or absence of mast cells may play some hitherto unsuspected rôle in the pathogenesis of atherosclerosis.

Various factors may be responsible for interference with the ester-splitting mechanism. Of these factors age, heredity and strain, particularly hypertension, deserve consideration. (1) Atherosclerosis is a degenerative process associated with advancing years which in one way seems as natural as the graying of the hair. It is the end of a song that is sung in the cradle. As Clifford Allbutt remarks: "It cannot be supposed that the stealthy hours carry away no qualities of tissue, no quantities of energy." The older the person the more likely is there to be marked atheroma. But in persons over eighty years of age the aorta may show hardly a trace of atheroma, whereas it may be present in the young. It is possible that it is the elastic fibers of the media which are damaged by the ageing process, and that the loss of elasticity may lead to degeneration of the intima. The fine vessels supplying the deeper layer of the intima have no muscular coat, and are dependent on the contractility of the aorta for a continuous flow of blood through their channels. (2) Heredity certainly plays a part.

Mortensen, in an analysis of 300 cases of atherosclerosis, found a family history in 67.5 per cent, and many of the remainder did not know the cause of death of their ancestors. O'Hare obtained a positive family history in 68 per cent of cases. One patient, whose father died of apoplexy and mother of cardiovascular-renal disease, had 9 brothers and sisters all of whom had died of apoplexy, and he himself had already had a stroke. (3) Hypertension is a difficult factor to assess, because it is common in the same age period as atheroma, and the association may be incidental rather than causal. Moreover, different sites must be considered separately. No accurate statistical data are available, but the following generalization appears justifiable: no causal connection in atheroma of the aorta, frequently connection in coronary atheroma, probable connection in cerebral atheroma. In coarctation of the aorta in young people there may be marked

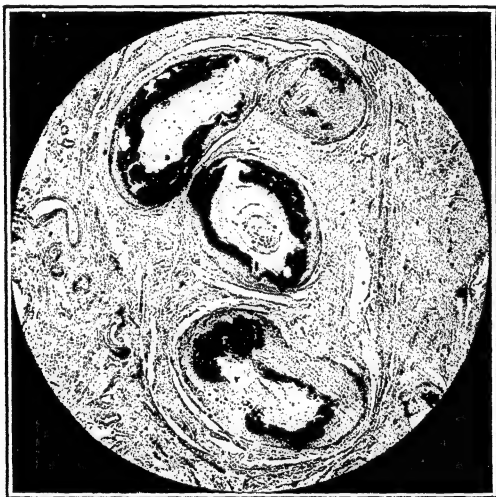


FIG. 194.—Mönckeberg's sclerosis of ovarian vessels. In the media of three of the arteries there is a large deposit and in the fourth a small deposit of lime salts.  $\times 16$ .

atheroma above the point of narrowing, and lesser degrees are common in the pulmonary artery in mitral stenosis. Prolonged experimental hypertension in the rabbit (an unsatisfactory animal for atheroma experiments) leads to the formation of atheromatous plaques in the aorta (Dill and Isenhour). In these cases there is no elevation of the blood cholesterol. Aortic lesions are nearly always most pronounced at points which may be considered specially subject to strain, such as the bifurcation of the aorta and the sites of origin of the intercostal and lumbar arteries. Winternitz believes that atheroma is closely associated with interference with the blood supply of subintimal areas by injury to the vasa vasorum which enter this region. This would agree with Hueper's theory of anoxia as a cause of the various forms of arteriosclerosis. The anoxia, which may be produced by a variety of chemical and physical agents, interferes with the oxidation mechanism and nutrition of the vessel wall.



The esterase mechanism may be under chemical or hormonal control. This is suggested by the fact that the cholesterosis of the aorta produced in rabbits by feeding cholesterol is prevented by the administration not only of thyroid gland, but also of iodine. It is said that thyroidectomy causes marked increase in the blood cholesterol, and it is well known that the level is high in myxedema. The incidence of atheroma in Iceland is remarkably low (Dungal), and it has been suggested that this may be due to the abundant iodine supply in the food, soil and air of that country. Atheroma is also very uncommon in China, as are other conditions involving disturbance of lipid metabolism. The facts of geographic pathology are always of interest, but fact must be distinguished from theory, and it is wise not to let fancy run too free in suggesting explanations. Possibly the temporary lipid deposits in the intima which are met with in adolescence may be due to transient inhibition of esterase due to hormonal imbalance.

**2. Medial Sclerosis of Mönckeberg.**—This is the type of arteriosclerosis which is observed by the clinician when he feels the arteries, for it is the vessels of the limbs, arteries of the muscular type, which are affected. The pipe-stem radials, the tortuous and prominent temporals, belong to this class. The condition is a senile degenerative change with no relation to high blood-pressure, although the long-continued administration of adrenalin in animals leads to calcification of the media. In these respects it resembles atheroma. The two lesions may both be present in the same artery. What relation, if any, it bears to atheroma it is not safe at present to say. The arteries most affected are the femoral, popliteal, the radial just above the wrist, and the parietal vessels such as the gluteal and pudendal. The visceral arteries (mesenteric, etc.) are seldom involved, but typical examples may be seen in the uterus and ovary in old persons.

**LESIONS.**—It is probable that the first change is fatty degeneration of the media. Calcium is then deposited in the degenerated tissue, and the vessel becomes hard and brittle.

The chief *microscopic* change is in the media (Fig. 194). The muscle fibers undergo fatty changes with degeneration, fragmentation, and the deposition of lime salts. These may be in the form of fine granules or large masses. Bone containing bone-marrow has sometimes been observed. The other coats are often normal, in which case there will be no narrowing of the lumen. Atheroma is often added, and this may produce marked occlusion, a change seen in senile and diabetic gangrene of the leg.

**MEDIONECROSIS OF THE AORTA.**—With advancing years the aorta often develops a basophilic mucin-like substance in the interstitial tissue of the media which stains blue with hematoxylin, intensely blue with colloidal iron, and gives a polychromatic (violet) reaction with such basic aniline dyes as thionin and toluidin blue. This polychromatic material represents a change in the mucopolysaccharide (hyaluronic acid) of the ground substance. The chromatropic material presents a vacuolated and even bubbly appearance (Fig. 195), the elastic tissue may be largely replaced, and focal necrosis may develop, especially in the inner and middle thirds of the wall. Cyst formation may occur in these necrotic patches, the idiopathic cystic medionecrosis of the aorta first described by Erdheim. The result of these changes, which can only be appreciated if the sections are stained for elastic tissue and with a stain for mucopolysaccharide, is to weaken the wall of the aorta to such a degree that a dissecting aneurism may develop or in rare cases spontaneous rupture of the

aorta. The pathologist sometimes encounters at autopsy cases of great cardiac hypertrophy with no obvious explanation such as arterial hypertension or aortic valvular disease. In a number of such instances I have seen marked medionecrosis with disappearance of elastic tissue and in one case a loud aortic diastolic murmur was heard, suggesting that the cardiac hypertrophy might be due to aortic insufficiency.

**3. Diffuse Arteriolar Sclerosis.**—This form of arterial degeneration is also called arteriolosclerosis and diffuse hyperplastic sclerosis. The term arteriole is vague and not susceptible of strict definition. In the present connection it is used to indicate the smaller arteries of the viscera, the intimate vasculature, vessels 100 microns in diameter or less. The lesions are not all of one type, but in general they cause thickening of the wall and narrowing of the lumen. Arteriolar sclerosis may be widespread, but is most frequent in the spleen, pancreas, kidney and adrenal. The arteries involved are of a smaller order than the "small" arteries affected by atheroma, *e. g.*, coronary and cerebral vessels.

Hypertension and the aging process seem to be the two principal etiological factors. That hypertension is a causal agent is indicated by the fact that identical lesions are found in the experimental hypertensive animal. On the other hand similar lesions, although usually less pronounced, may be present in persons without hypertension, especially in the aged. Hypertension appears to accentuate and speed up a normal wear-and-tear degenerative process.

**Hypertension** is at present divided into two forms, primary and secondary. The primary, which is by far the more common, is also called essential or idiopathic because the causation is unknown. In the secondary form there is some associated lesion such as chronic nephritis or adrenal cortical tumor which is presumed to bear a causal relationship to the hypertension. Renal ischemia, either due to disease or produced experimentally by Goldblatt's method of constricting the renal arteries, is constantly associated with hypertension. The kidney seems to exercise a control in the maintenance of normal blood pressure levels. Hypertension may, therefore, be due to a failure of this normal function, and not, as is commonly believed, to the liberation of a pressure substance as the result of ischemia. Dogs from whom both kidneys have been removed and who have been kept alive for seventy days by peritoneal lavage have developed sustained hypertension (Grollman *et al.*). It is evident that hypertension can occur in the absence of renal tissue, and that the presence of renal tissue may prevent rather than cause it. The Friedmans have suggested that the maintenance of normal pressure depends on a correct balance between the production of a pressor material by the adrenal cortex and its handling by the kidney. The administration of adrenal cortical extract or of desoxycorticosterone (DOCA) results in hypertension in the experimental animal. Thus hypertension may be the result either of renal failure or of adrenal overactivity, and it is possible that in the future the distinction between primary and secondary hypertension may lose its meaning. Essential hypertension, which constitutes 90 per cent of all cases of hypertension, may be divided into so-called benign and malignant forms. The benign form is characterized by a gradual onset and a long-continued course often of many years. The malignant form, very much less common, is frequently of abrupt onset

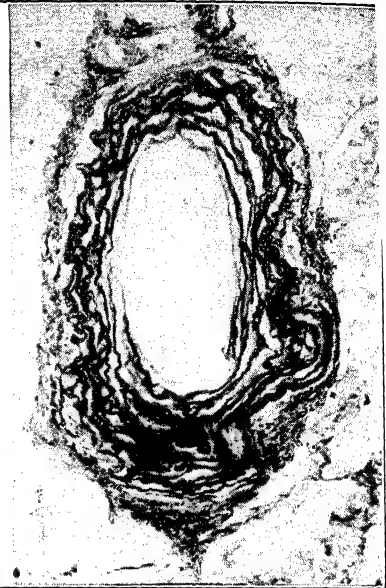
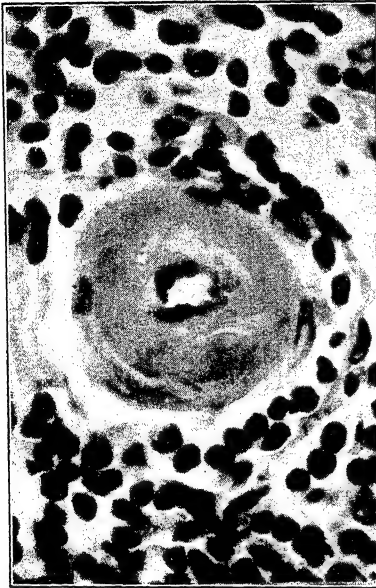
and runs a course measured in months rather than years. It often ends with renal failure (uremia), but not necessarily so. The lesions of hypertensive arteriolosclerosis differ in the two forms, although the distinction between the two is not always as sharp as indicated here. In each form there may be two significant lesions.

**BENIGN FORM.**—The characteristic lesions are hyaline degeneration and elastic hyperplasia. *Hyaline degeneration*, the commonest manifestation of arteriolosclerosis, is best seen in the smallest vessels, such as the afferent arterioles of the kidney, although not confined to these vessels. There is a sharply defined, smooth, acidophilic thickening of the subintimal tissue. In course of time the change may involve the entire thickness of the wall (Fig. 196), but some trace of nuclear structure usually remains. The appearance suggests an accumulation or deposition of hyaline material which leads to narrowing and in extreme cases to complete obliteration of the lumen. Duguid and Anderson suggest that the process is not a primary degeneration of the wall, but rather a deposit of hematogenous origin in the lumen of the vessel, this material becoming covered by endothelium and incorporated in the vessel wall. In the spleen hyaline arteriolosclerosis is so common as to have no pathological significance. In the kidney it is almost invariably associated with hypertension, whereas in non-hypertensives the kidney is one of the organs least frequently involved. In no other organ is there this constant relationship between arteriolosclerosis and hypertension, but in such organs the lesions are more frequent and more severe in persons with hypertension. Hypertension is, therefore, the most important causal factor, but, except in the case of the kidney, it is not an essential factor.

*Elastic hyperplasia*, sometimes called *elastosis* is most marked in the larger arterioles and medium-sized arteries, but some degree of it can be seen even in the smallest vessels. The internal elastic lamina is split up into several layers, a process known as *reduplication* (Fig. 197). There may also be proliferation of endothelial cells which become intermingled with the new elastic fibers. At first the elastosis is confined to the intima, causing narrowing of the lumen, but as time goes on both intima and media



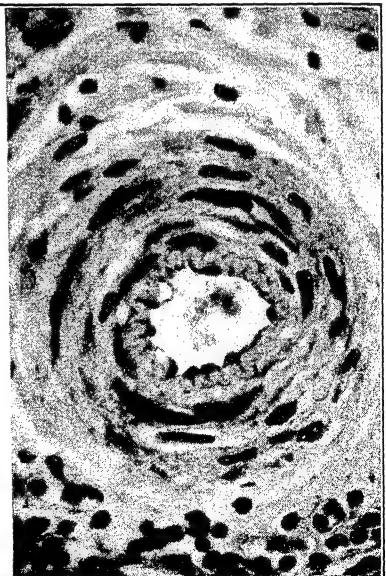
FIG. 195.—Medionecrosis of aorta, showing marked vacuolization of ground substance.  $\times 400$ .



### Benign

FIG. 196.—Hyaline degeneration.  
× 510.

FIG. 197.—Elastic hyperplasia.  
× 500.



### Malignant

FIG. 198.—Arteriolar necrosis.  
× 430.

FIG. 199.—Cellular hyperplasia.  
× 340.

FIGS. 196, 197, 198, 199.—ARTERIAL CHANGES IN HYPERTENSION.

are seen to be composed largely of elastic fibers in sections stained to show that tissue. The muscular type of artery has become converted into the elastic type characteristic of large arteries such as the aorta which are designed to withstand great strain and are little more than passive conducting tubes. The amount of elastic tissue in the walls of an artery approximately corresponds to the pressure of blood within it.

**MALIGNANT FORM.**—In the malignant form of hypertension, in which the process has a quickened *tempo* and the vessels have less time to adapt themselves to increased strain, the characteristic lesions in their order of importance are arteriolar necrosis and cellular hyperplasia. In *arteriolar necrosis*, also called necrotizing arteriolitis, the whole thickness of the vessel wall becomes necrotic and structureless (Fig. 198). The affected area stains diffusely red with eosin, and its limits are fuzzy and indistinct, as if it had been freshly painted and someone had smeared it with his thumb. This is in sharp contrast to the clean-cut smooth appearance of hyaline degeneration, in which sharply defined nuclei often persist. A rapid rise in blood-pressure is likely to lead to arteriolar necrosis due to the sudden and severe mechanical strain and extreme vasoconstriction. The lesion can be produced in the course of a few days in the experimental animal. The necrotic wall often becomes infiltrated with red cells, and hemorrhage is common, especially in the brain. Aneurismal dilatation can occur. Arteriolar necrosis is commonly seen in hypertension complicated by renal failure (uremia), and it is possible that toxic products in the blood may play a part in its production. *Cellular hyperplasia*, commonly called productive endarteritis and hyperplastic arteriosclerosis, is a condition in which the walls of the arterioles are thickened by a concentric cellular proliferation, so that they may present an "onion-skin" appearance (Fig. 199). The proliferation may be mainly subintimal, so as to merit the term endarteritis, but often the hyperplasia is most marked in the media, a natural response to the increased intravascular pressure. Without an elastic tissue stain it may be impossible to distinguish the limits of the nucleated thickened intima and the hyperplastic media. When the process is slower the nucleated appearance is lost and the new tissue becomes collagenous. Fatty degeneration may be marked in frozen sections. Elastic hyperplasia of the intima is not a special feature of the condition; such hyperplasia appears to be a reaction to gradually increasing and prolonged hypertension. It may, of course, be present in the medium-sized arteries of any one over middle age, but under these conditions it has no significance.

For the sake of convenience these four lesions have been described separately. They may, however, be combined and intermingled, for the slow (benign) form may have an acute (malignant) termination. Similar arteriolar lesions are seen in the hypertension of glomerulonephritis.

## ANEURISMS

An aneurism is a localized dilatation of an artery.

**CAUSES.**—Every aneurism is caused by weakening of the arterial wall. As a rule, it is the media which is damaged. Syphilis used to be the most important cause of aneurism of the large arteries. With the modern control of syphilis and with the increasing age of the population atheroma now

rivals or indeed exceeds syphilis as a causal factor. Syphilis seldom or never leads to aneurism formation in the small arteries, because in them the lesion is a diffuse thickening of the intima with little involvement of the media. An infected embolus will lead to suppuration of the vessel wall and destruction of the media so that an infective or *mycotic aneurism* is formed. Periarteritis nodosa may weaken the vessel and lead to the formation of multiple small aneurisms. Infection from an abscess or a tuberculous focus may form the starting-point of an aneurism. Finally, congenital weakness of the media in the arteries at the base of the brain has been suggested as a cause of a *congenital aneurism*.

VARIETIES.—A *true aneurism* is one in which the sac is formed by the wall of the vessel. A *false aneurism* is one in which the sac is formed by the surrounding tissues. It is caused by the rupture of a vessel, and is a hematoma rather than an aneurism. A *fusiform aneurism* is a dilatation of a segment of the vessel, and is seen in the aorta and its large branches. A *saccular aneurism* is a pouching of the vessel at one point. This is the usual form of aneurism. A *traumatic aneurism* is a false aneurism, a hematoma, formed by laceration of the vessel wall.

An *arteriovenous aneurism* is an abnormal communication between an artery and a vein, usually due to simultaneous laceration of an adjoining artery and vein. The blood passes from the artery into the vein, and produces a local distention of the vein which pulsates as forcibly as the artery.

A *congenital arteriovenous fistula* is a direct "shunt" between an artery and a vein without the interposition of capillaries. The blood passes forcibly into the vein, which becomes dilated (arteriovenous varix). The lesion is commonest in the leg, but may occur in the arm or the scalp; in the latter position, it forms a mass of dilated vessels known as a *cirsoid aneurism*. The clinical features are striking and make recognition easy: (1) higher blood-pressure and temperature in the affected limb; (2) increased circumference of the limb and the presence of bruits and thrills; (3) cardiac hypertrophy; (4) venous blood is redder on the affected side (pathognomonic); (5) roentgen-ray visualization of the fistula after the injection of thorotrast (arteriography).

A *dissecting aneurism* is not a true aneurism, *i. e.*, the vessel is not dilated. A hemorrhage occurs in the media of the aorta between the middle and outer thirds, commencing at the base and spreading along the vessel for a variable distance, splitting the media into two layers in its passage (Fig. 200). The blood tends to encircle the aorta, and may pass along its entire length to the bifurcation. In one of my cases the blood had dissected its way along the renal, splenic and superior mesenteric arteries causing gangrene of the bowel through pressure on the latter vessel. There may be ischemic necrosis of various tissues due to the blood in the wall of the aorta compressing the exit of arterial branches, as, for instance, in the case of the spinal arteries. On this account there may be a confusing multiplicity of symptoms. Usually the blood ruptures externally, with death to the patient, but it may rupture into the lumen. Should the patient survive, the blood may be absorbed, and two tubes are formed, one inside the other. Dissecting aneurism is a disease of later life, and is rare before the age of fifty years. The primary lesion in the great majority of cases is marked medionecrosis of the aorta causing rupture of the vasa vasorum, but

I have seen an occasional instance of blood entering the media through an atheromatous crack in the intima. As a rule a tear in the intima (especially at the spot where the latter is normal) is an effect rather than a cause of the condition. Syphilis is not a factor of any importance. There may be large collections of lymphocytes and plasma cells in the adventitia; this is not the result of syphilis, but is due, apparently, to irritation produced by the accumulation of red blood cells in the wall of the aorta. The blood-pressure is usually high unless the patient is *in extremis*, and the heart is correspondingly enlarged. The *symptoms* are characteristic. The patient is seized by a sudden sharp pain in the chest, accompanied by prostration. He often experiences what he describes as a tearing sensation. The pain passes off, but in a typical case death occurs some days later from the bursting of the aneurism into the pericardial sac, the chest, or the abdominal cavity.

**Aneurism of the Aorta.**—Aortic aneurism is so much more common and important than the other forms that it will be considered separately. Syphilis, especially in the thoracic aorta, used to be far the commonest etiological factor, as it is a great destroyer of elastic tissue (Fig. 201). Syphilitic aortitis is now much less frequent, but atheroma of the abdominal aorta, which causes a more diffuse disintegration of elastic fibers, seems to be taking its place. Each time the aorta dilates it does not quite return to the normal size owing to destruction of the elastic tissue. A syphilitic aneurism is more likely to be saccular; an atheromatous aneurism to be fusiform. The description which follows applies to the syphilitic form.

The dilatation begins in the ascending aorta or the arch (Fig. 202).

Usually it is localized (saccular aneurism), but sometimes it is more uniform (diffuse aneurism). The mouth has a smooth rolled edge. The aneurism may grow forward, eroding the sternum, or backward, eroding the bodies of the vertebræ (though not the intervertebral disks), causing great pain in the back. It may press on the trachea with difficulty in breathing, on the esophagus with difficulty in swallowing, on the left recurrent laryngeal nerve with hoarseness and aphonia. It may rupture on the surface, or into the trachea, bronchi, esophagus, pericardium, or pleural cavity.

The adjoining parts of the aorta show the characteristic wrinkling of syphilitic aortitis, but in the aneurismal sac the direct evidence of syphilis



FIG. 200.—Dissecting aneurism of the aorta. The media of the ascending aorta has been split into two layers. The dark mass between the layers is blood.



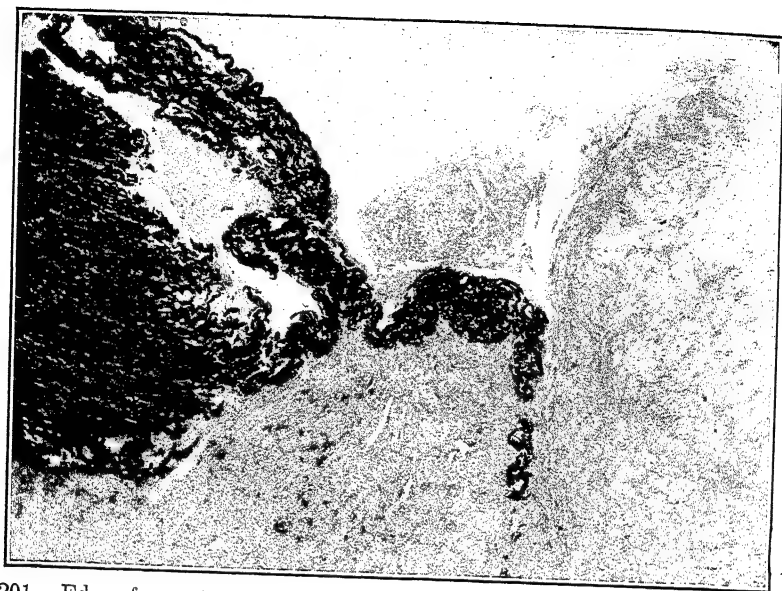


FIG. 201.—Edge of aneurism of aorta, showing how the elastic tissue (black) suddenly ceases. Elastic tissue stain.  $\times 75$ .



FIG. 202.—Aortic aneurism. The rolled edge is well seen, as well as the characteristic nodular appearance of syphilitic aortitis. The aortic cusps are normal.  
(370)



is usually obscured by atheroma. Thrombosis occurs on the roughened lining, and layer after layer of clot is laid down and becomes incorporated with the wall of the sac. The clot therefore shows a characteristically laminated appearance. Microscopic examination of the wall of the sac shows that it consists only of adventitia; the intima and media have disappeared. Adjoining parts of the wall show the microscopic lesions of active syphilitic aortitis.

**ANGIOSPASTIC DISEASES.**—The muscular walls of the arterioles are supplied both with constrictor and dilator fibers. In inflammatory conditions of arteries such as Buerger's disease the lesion irritates the sensory sympathetic fibers and thus causes constriction of the anastomotic and terminal arteries. For this reason operative procedures designed to paralyze the sympathetic may be of great benefit by increasing the collateral circulation. Recent embolism and rapid thrombosis have a similar action on the sympathetic. In advanced non-inflammatory arterial occlusion (arteriosclerotic) there is inhibition of vasoconstrictor tonus, so that no benefit is obtained by paralyzing the sympathetic. *Raynaud's disease* is a condition of long-continued arterial spasm resulting in local asphyxia and symmetrical gangrene. It usually affects the fingers. It is generally believed that the essential cause is a disturbance of the vasomotor mechanism, although it has been suggested that there is some local fault in the periphery independent of the vasomotor mechanism (Lewis). Mild cases of angiospasm ("dead fingers") are very common; they occur usually in women. Vasodilatation is the basis of *erythromelalgia* (*erythros*, red; *melos*, limb; *algos*, pain), a condition marked by a paroxysmal throbbing and burning pain usually in the feet, sometimes in the hands, accompanied by a dusky mottled redness of the parts.

## THE VEINS

### PHLEBITIS

Inflammation of a vein or phlebitis differs from inflammation of an artery in the greater tendency to thrombosis and the correspondingly lessened tendency to hemorrhage. The inflammation may be suppurative or non-suppurative.

**SUPPURATIVE PHLEBITIS.**—The inflammation is caused by pyogenic bacteria which usually invade the vein from without. A vein passing through an abscess or an area of cellulitis is much more likely to become inflamed and thrombosed than is the corresponding artery. The entire thickness of the wall is invaded by leucocytes and thrombosis rapidly occurs, so that the condition may be called a thrombophlebitis. The thrombus becomes septic, softens, and is likely to disintegrate with the formation of emboli. Hemorrhage is not common, because the thrombosis advances ahead of the inflammation and closes the vessel. Some of the most important examples of suppurative thrombophlebitis are as follows: phlebitis of the lateral sinus following acute otitis media and threatening to extend down the jugular vein; phlebitis of the facial veins following a boil or carbuncle of the nose or upper lip extending through the ophthalmic veins to the cavernous sinus; phlebitis of varicose hemorrhoidal veins (piles); phlebitis extending from the appendix to the portal vein and causing a portal pyemia; phlebitis of the pelvic and femoral veins following puerperal sepsis or operations on the female pelvic organs; phlebitis of varicose veins of the leg when ulceration has occurred. In all of these instances the great danger is that multiple septic embolism may occur and a condition of pyemia be set up.

**NON-SUPPURATIVE PHLEBITIS.**—When a vein is ligatured an aseptic phlebitis occurs accompanied by thrombosis. Owing to the absence of infection the thrombus is invaded by capillaries and fibroblasts and organized into fibrous tissue. The presence of a thrombus is of itself sufficient to produce an inflammatory reaction in the vein wall. This is apt to be mistaken for a primary inflammation, and the condition is wrongly labelled thrombophlebitis.

**THROMBOPHLEBITIS MIGRANS.**—Migrating thrombophlebitis is an unusual disease of the circulatory system characterized by repeated venous thromboses, now one, now another short segment of vein being involved in different parts of the body, often in recurring attacks extending over a period of months or even years. It may occur at any age. Birnberg and Hansen report a case in a boy fourteen years of age, in whom inflamed veins were observed in both legs and on both sides of the abdominal wall. At autopsy the entire small bowel was gangrenous, and old thrombi were present in the vena cava, splenic vein and hemorrhoidal veins. I have seen a rather similar case in a young man at the Vancouver General Hospital with thrombosis in the veins of the legs and the cranial cavity. A correct diagnosis was made by the neurologist.

There is a curious relation between the condition and intraabdominal malignancy, usually of the pancreas, less frequently of the stomach. The great Trousseau observed and recorded the condition in himself when he was dying of carcinoma of the pancreas, so that the term Trousseau's syndrome has been fittingly applied to the association. This may be due to release of trypsin, which has a thromboplastic action, from the disrupted glandular tissue of the tumor bed (Gore). Even secondary growths of the pancreas may produce this effect. In about 50 per cent of the cases the condition may be called idiopathic, there being no associated tumor. These cases may be expected to recover.

## PHLEBOSCLEROSIS

The condition of phleboscclerosis or phlebofibrosis is not uncommon, although seldom recognized because seldom looked for. It does not appear to be related to arteriosclerosis, for it occurs at an earlier period of life, being commonest in young men between twenty and thirty years of age; it is not associated with fatty degeneration or calcification; and it bears no relation to hypertension. It affects chiefly the veins of the legs, where the affected vessels feel like hard mobile cords, which may be mistaken for tendons. There are no associated symptoms. It is a disseminated lesion affecting both superficial and deep veins and is always bilateral. It has been called endophlebitis and hyperplastic phlebitis, but it is a degenerative and not an inflammatory condition. The affected vein is thickened and the lumen narrowed. The chief microscopic change is a marked increase of the connective tissue of the media and corresponding atrophy of the muscle fibers, together with a lesser fibrosis of the intima. The innermost layers of the thickened intima are hyaline, and the endothelial lining is missing. The distinction between the coats of the vessel is largely lost. The exact nature of the condition is uncertain and the cause is quite unknown.

## VARICOSE VEINS

A varix or varicose vein is one that is dilated, lengthened, and tortuous. The three common sites are: (1) The veins of the leg, especially the internal saphenous; (2) the hemorrhoidal veins (hemorrhoids or piles); (3) the pampiniform plexus of the spermatic cord (varicocele).

**CAUSES.**—These may be predisposing and exciting. An important *predisposing* cause appears to be a congenital and inherited weakness of the walls and valves of the veins. The condition may run in a family for generations, and the same vein may be affected each time. The *exciting* factor is an increase of pressure in the vein, and may be caused in the following ways: (1) Central obstruction to the venous return (mitral stenosis, emphysema, cirrhosis of the liver). (2) Pressure of a tumor, gravid uterus, or loaded rectum. (3) Prolonged standing. (4) Straining and violent muscular effort. The former aggravates piles, while the latter explains the frequency of varicose veins of the legs in athletes.

**LESIONS.**—The valves give way, and the vein becomes dilated, elongated and tortuous. A phlebosclerosis develops. At first there is hypertrophy of the media from increased strain, followed later by atrophy and replacement fibrosis. The intima and adventitia also become fibrosed and thickened. The thickening is irregular, and pouching of the wall occurs in the intervals. Thrombosis in these pouches is very common.

**EFFECTS.**—The effects are felt by the veins and the tissues which they drain. Hemorrhage, phlebitis, and thrombosis are the important venous complications. Hemorrhage is commonest in the case of piles, where the veins are covered only by mucous membrane (hence the name hemorrhoids). There may be hemorrhage from the veins of the leg as the result of trauma or ulceration of the overlying tissue. The hemorrhage may be into the tissue or on the surface. The presence of ulceration naturally predisposes to infection and thrombosis.

The *tissues* suffer severely as the result of the varicosity. There is chronic congestion and the circulation is greatly interfered with. Edema is apt to develop, probably as the result of an associated lymphangitis, the overlying skin becomes sodden and devitalized and atrophic from pressure, and a varicose ulcer may be formed, usually on the lower third of the leg. This type of ulcer is likely to be very chronic, and may heal and break down repeatedly, causing great disability and suffering to the patient. The skin of the lower part of the leg acquires a mahogany-brown color, due to pigmentation from repeated small hemorrhages into the tissues. The modern treatment of varicose veins and varicose ulcers has completely changed the previously rather gloomy outlook.

### ADDITIONAL READING

- Angiospastic Conditions.** LEWIS: *Heart*, 1929, 15, 8. REID AND HERRMANN: *Ann. Surg.*, 1935, 102, 321. SCOTT: *Ann. Surg.*, 1935, 102, 331.
- Arterial Changes in Hypertension.** BELL AND CLAWSON: *Arch. Path.*, 1928, 5, 939. GOLDBLATT: *J. Exper. Med.*, 1934, 59, 347; 1937, 65, 671. MORITZ AND OLDT: *Am. J. Path.*, 1937, 13, 679.
- Arteriosclerosis.** BEITZKE: *Virchows Arch. f. path. Anat.*, 1928, 267, 625; 1929, 275, 532. DUFF: *Arch. Path.*, 1935, 20, 81, 259. DUGUID AND ANDERSON: *J. Path. and Bact.*, 1952, 64, 519. HUEPER: *Arch. Path.*, 1944, 38, 162. JONES: *Virchows Arch. f. path. Anat.*, 1904, 178, 567. MOSHCOWITZ: *Vascular Sclerosis with Special Reference to Arteriosclerosis*, New York, 1942.
- Arteriovenous Aneurism.** HOLMAN: *Arteriovenous Aneurism*, New York, 1937.
- Atherosclerosis.** BLUMENTHAL, *et al.*: *Am. J. Path.*, 1944, 20, 665. *Am. J. Path.*, 1950, 26, 989. CRAWFORD AND LEVENE: *J. Path. and Bact.*, 1952, 64, 523. DUFF: *Arch. Path.*, 1935, 20, 81 and 259. DUFF AND McMILLAN: *Am. J. Med.*, 1951, 11, 92. DUGUID: *J. Path. and Bact.*, 1926, 29, 371; *J. Path. & Bact.*, 1948, 60, 57. DUNGLA: *Lancet*, 1936, 1, 1354. GOFMAN *et al.*: *Science*, 1950, 111, 166. *Circulation*, 1952, 5, 119. JONES, GOFMAN, *et al.*: *Am. J. Med.*, 1951, 11, 358. LEARY: *Am. Heart J.*,

- 1935, 10, 328; Arch. Path., 1941, 32, 507. Arch. Path., 1949, 47, 1. McLEITCHIE: Am. J. Path., 1952, 28, 413. PAGE: Ann. Int. Med., 1941, 14, 1741. RINEHART AND ABUL-HAJ: Arch. Path., 1951, 52, 189. SAPHIR AND GORE: Arch. Path., 1950, 49, 418. TAYLOR: Am. J. Path. 1953, 29, 589. WILLIS: Can. Med. Assn. Jour., 1952, 67, 644. WILENS: Am. J. Path., 1951, 27, 825. WINTERNITZ *et al.*: The Biology of Arteriosclerosis, Springfield, Ill., 1938.
- Ayerza's Disease.** CHENEY: Am. J. Med. Sci., 1927, 174, 34. LEOPOLD: Am. J. Med. Sc., 1950, 219, 152.
- Ceroid in Atherosclerosis.** HARTROFT: Am. J. Path., 1952, 28, 526.
- Coarctation of Aorta.** FRAY: Am. J. Roent., 1930, 24, 349.
- Collagen Disease.** AEGERTER AND LONG: Am. J. Med. Sc., 1949, 218, 324. DUFF: Canad. M. A. J., 1948, 58, 317. KLEMPERER: Am. J. Path., 1950, 26, 505. KLINGE: Ergebn. d. allg. Path. u. path. Anat., 1933, 27, 1.
- Dermatomyositis.** PAGEL *et al.*: J. Path. and Bact., 1949, 61, 403.
- Dissecting Aneurism.** HOLLAND AND BAYLEY: Am. Heart J., 1940, 20, 223. SAILER: Arch. Path., 1942, 33, 704. SHENNAN: Great Brit. Med. Res. Council, Spec. Rep. Series, No. 193, London, 1934. TYSON: Am. J. Path., 1931, 7, 581.
- Disseminated Lupus Erythematosus.** CHURG AND GRISHMAN: Am. J. Path., 1953, 29, 199. GITLOW AND GOLDMARK: Ann. Int. Med., 1939, 13, 1046. KLEMPERER in McManus' Progress in Fundamental Medicine, Philadelphia, 1952. KLEMPERER, *et al.*: Arch. Path., 1941, 32, 569. ROSE AND PILLSBURY: Ann. Int. Med., 1938, 12, 951.
- Fibrinoid Degeneration.** GLYNN AND LOEWI: J. Path. and Bact., 1952, 64, 329.
- Hypertension.** FRIEDMAN AND FRIEDMAN: Can. Med. Ass'n. J., 1949, 61, 596.
- Lupus Erythematosus Cell.** BERMAN, *et al.*: Am. J. Clin. Path., 1950, 20, 403. HARGRAVES, *et al.*: Proc. Staff Meet., Mayo Clinic, 1948, 23, 25.
- Macromolecules in Atheroma.** GOFMAN, *et al.*: Science, 1950, 111, 166. Yearbook of Pathology and Clinical Pathology, 1951, p. 110.
- Medial Ischemia and Atheroma.** SCHLICHTER, *et al.*: Am. J. Med. Sc., 1949, 218, 603.
- Medionecrosis of Aorta.** ERDHEIM: Virchows Arch. f. path. Anat., 1930, 276, 187. MORITZ: Am. J. Path., 1932, 8, 717.
- Paramyloidosis in Disseminated Lupus.** TEILUM: Am. J. Path., 1948, 24, 409.
- Periarteritis Nodosa.** ARKIN: Am. J. Path., 1930, 6, 401. DAVSON, *et al.*: Quart. J. Med., 1948, 17, 175. GORE: Am. J. Path., 1950, 26, 155. KERNOHAN AND WOLTMAN: Arch. Neurol. and Psychiat., 1938, 39, 655. KLOTZ, J. Med. Res., 1917, 37, 1. PAGEL: Jour. Clin. Path., 1951, 4, 137. RICH: Bull. Johns Hopkins Hosp., 1942, 71, 123. RICH AND GREGORY: Bull. Johns Hopkins Hosp., 1943, 72, 65.
- Phlebosclerosis.** HAUSWIRTH AND EISENBERG: Arch. Path., 1931, 11, 857. LEV AND SAPHIR: Arch. Path., 1951, 51, 154.
- Primary Idiopathic Thrombophlebitis.** BARKER: Arch. Int. Med., 1936, 58, 147. D'ABREU: Brit. M. J., 1934, 1, 101.
- Rheumatic Arteritis.** VON GLAHN AND PAPPENHEIMER: Am. J. Path., 1926, 2, 235.
- Syphilitic Aortitis.** MARTLAND: Am. Heart J., 1930, 6, 3.
- Temporal Arteritis.** CARDELL AND HANLEY: J. Path. and Bact., 1951, 63, 587. COOKE, *et al.*: Quart. J. Med., 1946, 15, 47. GILMOUR: J. Path. and Bact., 1941, 53, 263. HORTON, *et al.*: Proc. Staff Meet., Mayo Clinic, 1932, 7, 700.
- Thrombo-angiitis Obliterans.** BARRON AND LINENTHAL: Arch. Surg., 1929, 19, 735. HORTON AND BROWN: Arch. Int. Med., 1932, 50, 884. HORTON AND DORSEY: Arch. Path., 1932, 13, 910.
- Thrombophlebitis Migrans.** BIRNBERG AND HANSEN: J. Pediat., 1942, 21, 775.
- Trousseau's Syndrome.** GORE: Am. J. Path., 1953, 29, 613.

## THE RESPIRATORY SYSTEM

## THE NOSE

**Granulomata.**—Many granulomatous infections may involve the nose, but the only common one is syphilis. They all show a formation of new tissue, followed by necrosis, ulceration, and destruction of the septum.

**SYPHILIS.**—Syphilis of the nose used to be common. It may be congenital or acquired. The *congenital* form may cause an atrophic rhinitis with foul-smelling discharge. Or it may destroy the septum, cartilage, and bone so that the bridge falls in, giving the *saddle nose* so characteristic of congenital syphilis. The *acquired* tertiary lesion is a gumma which perforates the septum and may destroy the bridge of the nose so as to give the more uncommon "saddle nose" of acquired syphilis.

**TUBERCULOSIS.**—Tuberculosis of the nose is rare, and is usually a complication of pulmonary tuberculosis. It is likely to produce an ulcerative lesion of the cartilaginous part of the septum.

**LEPROSY.**—Leprosy starts as a nodule which enlarges, undergoes ulceration, and may cause perforation of the septum.

**RHINOSCLEROMA.**—Rhinoscleroma is a disease of inhabitants of Eastern Europe. As the name implies, the lesion of the nose is peculiarly hard. The condition commences in the nose, but tends to spread to the pharynx. It is at first proliferative and then destructive. The characteristic Mikulicz cells and other microscopic features are described in Chapter 7.

**GLANDERS.**—Glanders is a very rare infection of the nose in man, although common in the horse. As usual, there is proliferation followed by destruction. The glanders bacilli are present in the secretion. The bacteriology and pathological lesions are given in Chapter 7.

**MALIGNANT GRANULOMA.**—This rare, terrible and little understood disease may occur at any age. Following a prolonged prodromal period characterized by stuffiness of the nose, an ulcer develops on the nostril or nasal septum which slowly increases in size until the bones of the face and the palate are destroyed and death ensues from meningitis or bronchopneumonia. The final picture is one of hideous disfigurement of the face and erosion of the skull and large arteries.

The microscopic lesions are granulomatous in type with epithelioid cells, giant cells and lymphocytes, but the most striking feature is intense necrosis resembling that of an infarct and possibly due to a marked degree of obliterating arteritis which accompanies the condition. Similar lesions have been found in the viscera, as well as necrotizing arteriolitis and glomerulonephritis (McCart). In spite of its name, which it owes to its relentless progress, there is no microscopic evidence of malignant neoplasia. The cause is unknown, possibly a virus or a local tissue hypersensitivity.

**TUMORS.**—Tumors of the nasal cavity are usually polypoid in type. The commonest form of nasal polyp is not really a tumor, but an edematous mass of in-

flamed and hypertrophied mucous membrane. It is usually attached to the lateral wall near the opening of the antrum of Highmore, and hangs down as a soft mucoid globular mass with a well-defined pedicle. Sometimes a proliferation of mucous glands may suggest an adenoma. Carcinoma is uncommon and sarcoma still more rare.

## THE LARYNX

### LARYNGITIS

Infections of the nasopharynx will readily spread down and infections of the bronchi spread up to the larynx. We may recognize the following forms of laryngitis: simple, diphtheritic, tuberculous, and syphilitic.

**Simple Laryngitis.**—The inflammation is usually *acute*. It may form part of a common cold or may occur in the course of one of the infectious fevers, especially measles and scarlet fever. Pneumococci, streptococci, and *Micrococcus catarrhalis* are the commonest organisms. Non-bacterial irritants such as steam and chlorine gas may cause violent inflammation. The lesions are those of acute inflammation of any mucous membrane. The membrane is swollen and congested and is covered by mucus poured out by the glands. Microscopically it is infiltrated with inflammatory cells.

**Chronic laryngitis** may be caused by excessive smoking, chronic alcoholism, or undue use of the vocal cords. The surface of the mucous membrane is dry and covered by small papillary projections. The epithelium is thickened and opaque (pachydermia). The submucosa is infiltrated with chronic inflammatory cells. In typhoid fever there may be swelling of the lymphoid tissue of the larynx, and in rare cases ulceration of the cartilage.

**DIPHTHERITIC LARYNGITIS.**—Diphtheria is primarily a disease of the pharynx, but the infection frequently spreads to the larynx. A "false membrane" consisting of fibrin, leucocytes, and necrotic epithelial cells is formed on the surface, but is firmly attached to the underlying tissue. A membranous type of laryngitis may also occur in streptococcal and other severe infections.

**TUBERCULOUS LARYNGITIS.**—This is practically always secondary to pulmonary tuberculosis. It is fortunately not nearly as common as might be expected. Tubercles are formed in the subepithelial tissue. These undergo necrosis, and shallow lenticular ulcers are formed on the surface. The disease begins in the arytenoid region or the vocal cords, and may spread extensively so as to involve all other parts of the larynx. Eventually there may be widespread destruction of the cartilages and the epiglottis, a peculiarly distressing condition because food tends to pass down into the trachea and lungs.

**SYPHILITIC LARYNGITIS.**—In the secondary stage there may be catarrh or mucous patches. In the tertiary stage there is destruction followed by healing and scar formation. Papillary masses of new tissue may be formed. The scarring leads to distortion of the larynx, stenosis of the glottis, and a characteristic hoarseness of the voice.

### EDEMA OF THE GLOTTIS

Edema of the glottis occurs in the course of an acute inflammation such as diphtheria or that caused by the inhalation of steam, irritating gases, etc. It may be part of an angioneurotic edema, but seldom forms part of a general cardiac or renal edema. There is great swelling of the loose tissue

in the posterior wall of the pharynx, the false vocal cords, etc. The parts are very swollen and boggy. The edema may develop acutely and may cause death from suffocation.

### TUMORS OF THE LARYNX

**Papilloma.**—This is the commonest tumor of the larynx. It is a small warty growth composed of loose connective tissue, and usually arises from the vocal cords or the anterior commissure. It is common in singers and others who have to use the voice much. The tumor behaves differently in adults and children. In the adult it shows a strong tendency to recur after removal, and occasionally, though rarely, becomes malignant. In the child there is also a strong tendency to recur, no matter how radical the removal, but the new tumors are often at other sites in the larynx, and in time there is most likely to be spontaneous cure. In children, therefore, multiple recurrent papilloma is a benign self-limited disease.

**Nodular Fibroma.**—This is not uncommon in children. It is a small sessile growth composed of vascular connective tissue.

**Carcinoma.**—Cancer of the larynx is essentially a male disease, and often shows a definite relation to chronic irritation, such as overuse of the voice or abuse of tobacco and alcohol. Two forms may be recognized, intrinsic and extrinsic. The *intrinsic* form constitutes 80 per cent of the cases, and arises from the vocal cords, usually the anterior third. The tumor, originating from fully differentiated stratified squamous epithelium, often remains confined to the larynx for a considerable time, and offers a good chance of recovery after operative removal as well as being quite radiosensitive. The *extrinsic* form arises in the pyriform fossa, the aryepiglottic folds, or on the epiglottis itself. It involves the hypopharynx, invades the surrounding tissue, and gives rise to early lymph node metastases. This is one form of hypopharyngeal carcinoma. Carcinoma of the larynx begins as a small indurated patch or as a papillary tumor. In the later stages there is extensive destruction, ulceration, and sepsis with the danger of lung abscess or inhalation pneumonia. The intrinsic form is epidermoid, the extrinsic form usually transitional in type.

**Sarcoma.**—A rare tumor.

### THE BRONCHI

#### BRONCHITIS

**Acute Tracheobronchitis.**—Acute inflammation of the bronchi affects either the large bronchi and trachea or the small bronchioles. The latter condition is associated with pneumonia, while the former occurs in a pure form which may be called tracheobronchitis.

**ETIOLOGY.**—The irritant may be bacterial, mechanical, or toxic. The bacteriology of acute bronchitis is by no means certain, but it is probable that the pneumococcus, micrococcus catarrhalis, streptococcus, staphylococcus, and influenza bacillus may at different times be responsible. Their presence in the sputum does not prove that they have caused the inflam-

mation in the bronchial wall. Acute bronchitis may complicate any of the infectious fevers, especially the early stages of typhoid. Dust, steam, poisonous gases, and ether may all produce acute tracheobronchitis.

**LESIONS.**—The mucous membrane of the trachea and large bronchi is red, swollen, and covered with a tenacious exudate which may be mucoid or purulent. Microscopically the mucosa is greatly congested and infiltrated with leucocytes. It is remarkable how often the latter are of mononuclear rather than polymorphonuclear type. The ciliated epithelium may be desquamated and the mucous glands are distended with mucus and show marked catarrhal change. The lumen of the bronchus is filled with pus.

**CHRONIC BRONCHITIS.**—Chronic inflammation is a common condition, especially in damp climates. But it is seldom or never a primary entity, being rather a complication of some preëxisting pathological condition which may lie in the heart, the nasal sinuses, or the bronchi themselves.

*Chronic heart disease*, valvular or myocardial, is a common cause of chronic bronchitis on account of the continued congestion of the bronchial tree which weakens the resistance to bacterial invasion from the nose and throat. The *nasal sinuses* and *antrum* may serve as a constant source of infection, for septic material can so readily pass down the trachea and bronchi without ever being suspected.

*Dilatation of the bronchi* (bronchiectasis) is now known to be at the bottom of very many cases of chronic bronchitis, thanks to the diagnostic use of lipiodol. This subject will be discussed more fully in connection with septic diseases of the lung.

**Lesions.**—The mucous membrane may be swollen and hypertrophic, and bathed with mucus or pus. In old cases it may become atrophic, so that the wall has a reticulated appearance owing to strands of fibrous tissue which remains. Microscopically all the coats are infiltrated with round cells, but a replacement fibrosis which takes the place of the glands, muscle, and cartilage may be the chief feature. The epithelium is low and cubical, sometimes even flattened.

**FIBRINOUS BRONCHITIS.**—This is a rare and obscure condition in which the patient coughs up bronchial casts at periodic intervals. The casts are composed of mucin and epithelium rather than true fibrin. In diphtheria and pneumonia bronchial casts composed largely of fibrin may be formed.

## BRONCHIAL ASTHMA

The chief lesion in true asthmatics is a marked thickening of the wall of the smaller bronchi. All the coats are involved, but the muscular tissue is hypertrophied to a remarkable degree. The mucous glands are swollen and active, and the smaller bronchi may be blocked with mucus. During an anaphylactic attack the hypertrophied muscle is thrown into severe spasm, the lumen is narrowed, and expiration becomes very difficult. This difficulty is increased by the narrowing of the lumen caused by the general thickening of the wall and the abundant secretion of mucus. The walls are infiltrated with chronic inflammatory cells, mostly eosinophils but with many lymphocytes. Eosinophils are found in other conditions where hypersensitiveness plays a part (infection with animal parasites, skin disease, etc.), and their presence must indicate some kind of defense reaction. In some cases inflammatory lesions of the arteries have been observed



similar to those of periarteritis nodosa. This is not surprising, as both diseases have an allergic basis. A striking feature in many cases is great hyaline thickening of the basement membrane of the bronchial mucosa. When the patient dies in the acute attacks known as status asthmaticus numerous bronchi may be blocked by thick mucus and the mucous glands are active and distended with mucus. These plugs of mucus must contribute greatly to the respiratory difficulty and distress. The lung may show areas of emphysema and atelectasis, the former due to the great strain on the pulmonary tissue during the expiratory spasm, the latter due to absorption of air beyond bronchioles blocked by mucus. Elongated Charcot-Leyden crystals are often present in the sputum. They are believed to be derived from the eosinophils, and are also found in the tissues in leukemia and in the stools in amebic dysentery.

### THE LUNGS

**DESCRIPTIVE OUTLINE.**—In describing the lungs attention is paid to the pleura, pleural cavity, lung substance (color, air content, etc.), bronchi, pulmonary vessels, and bronchial lymph nodes. The *pleura* presents the usual smooth glistening surface of a serous membrane. The *pleural cavity* is nearly dry during life, but an appreciable amount of serous fluid may collect during a prolonged death agony, and in cardiac and renal disease there may be a remarkable accumulation during the last few hours of life. The lungs may be greater in *volume* than normal or they may be collapsed. The *weight* of the right lung is 350 to 550 grams, that of the left lung 325 to 450 grams. The *texture* is soft and pillowy. Owing to its *air content* it crepitates when pressed between the finger and thumb, and floats in water. These properties are lost when the air has been squeezed out of the lung by pressure from without or has been replaced by inflammatory exudate or edema. The apex should be inspected for the puckered scar of healed tuberculosis. The *color* depends on the amount of blood in the lung and on the amount of carbon pigment which has been inhaled. In the child the lung is of a uniform pink color, while in the adult it is a dark slate-gray and shows varying degrees of pigmentation. The pleural lymphatics contain carbon, and thus outline in black the polygonal lobules which give the surface a mosaic appearance. On the cut surface the pigmentation follows the lines of the septa, the bronchi, and the arteries, and blackens any patches of scar tissue which may be present. In actual practice it is rare to find a lung that is perfectly normal throughout in color and consistence, because during the last hours of life blood tends to collect in the loose pulmonary tissue, and even after death blood gravitates to the dependent part of the lung, rendering it darker and firmer than normal. The *bronchi* are opened, their wall inspected for inflammation or tumor, and any contents noted. The *pulmonary vessels* are opened and examined for thrombi or emboli. Finally the condition of the *bronchial lymph nodes* is noted.

### LOBAR PNEUMONIA

Pneumonia signifies an inflammatory consolidation of the lung. When it is diffuse it is called lobar pneumonia; when nodular in type it is known as bronchopneumonia. Pneumonias may also be classified on a bacteriological basis according to the infecting organism. Lobar pneumonia is a much more clear-cut pathological entity with constant etiology than is bronchopneumonia.

**ETIOLOGY.**—In over 95 per cent of cases the infecting organism is the pneumococcus. In the few remaining cases it is Friedländer's pneumobacillus, which produces a characteristic slimy type of exudate.

It is now believed by many observers that *allergy* plays an important part in the pathogenesis of pneumonia. Certain it is that the age period at which the disease is most prevalent is that at which there is a high level of humoral immunity. Clinical observations also suggest that previous infections of the respiratory tract may sensitize the lungs so that pneumonia may be the result of a subsequent infection.

*Predisposing factors* lower the resistance of the patient and allow the organisms to pass from the upper to the lower respiratory tract. The best recognized of these are profound fatigue, chill, injury to the chest, severe fractures, debilitating diseases, and chronic alcoholism.

**ROUTE OF INFECTION.**—Pneumococci reach the pulmonary alveoli *via* the bronchial tree. The organisms pass in the inflammatory fluid from one alveolus to another through the interalveolar pores of Cohn. Thus the wave of infection sweeps throughout an entire lobe, but is often limited to that lobe. Spread of infection along the bronchial tree under the control of gravity is also of primary importance. Direction of spread depends on the bodily attitude of the sick person or animal. The capsular polysaccharide contains an edema-producing substance which can be extracted. It is natural, therefore, that the first feature of the exudate should be a marked inflammatory edema.

The mechanism by which the pneumococci are destroyed has been demonstrated in a remarkably beautiful series of experiments by Barry Wood and his associates. The all-important element is the leucocyte, mainly polymorphonuclear, but macrophage in the later stages. The organisms are carried outward by the advancing flood of edema fluid, pursued in turn by the leucocytes. If the tortoise is to catch up with the hare the pace of the latter must be slowed down. This may be effected by means of specific antibodies which cause agglutination of the pneumococci or by the bacteriostatic action of the sulphonamides and antibiotics. When the leucocytes have overtaken the pneumococci they pin them against the walls of the alveolar sacs, and only then are they able to engulf them.

**SYMPTOMS.**—The clinical manifestations of lobar pneumonia are partly local, partly general. The former are pain in the chest made worse by breathing, signs of consolidation of the lung (dullness on percussion, blowing breathing, increased vocal fremitus and resonance), moist râles during the period of resolution, and blood-stained sputum. The general symptoms are fever, dyspnea, evidence of severe toxemia, and a marked leucocytosis. After a course of seven or eight days the illness suddenly terminates by crisis. Owing to the therapeutic revolution wrought by antibiotics it is seldom that the physician sees now the picture just described.

**Lesions.**—The essential pathological feature is an out-pouring of an inflammatory exudate into the alveoli in response to the irritation produced by the pneumococci. The alveoli are filled by this exudate, the air is displaced, and the lung or part of it is converted into a solid and airless organ. This process is known as consolidation or hepatization because the lung becomes like the liver (*hepar*) in consistence. Four stages are recognized for descriptive purposes: congestion, red hepatization, gray hepatization and resolution, but these are really of very little importance. What

is important is to realize that the process is a progressive one commencing at the hilus and sweeping out to the periphery, involving one or more lobes and sometimes both lungs. It follows that one part of the lung may be at one stage while another part is at another. The stage of the process can be determined by noting the freshness or the reverse of the exudate.



FIG. 203.—Lobar pneumonia. The upper lobe is completely consolidated, being in a state of gray hepatization. The lower lobe, only part of which is shown, is not involved.

The *gross appearance* is very characteristic (Fig. 203). In the untreated case by the end of the second day the affected part of the lung is consolidated, red, and sinks in water. It is friable, and the cut surface is rough and granular like red granite. Later it is gray and moister. The pleural surface is covered with a fibrinous exudate and the bronchial nodes are enlarged.

The microscopic picture also depends much on the stage of the process. At the beginning the capillaries are congested, and the alveoli are filled with edema fluid containing great numbers of pneumococci (Fig. 204). Soon fibrin is formed and polymorphonuclears appear in great numbers, together with red cells and a few lymphocytes. All the elements are sharp and distinct (Fig. 205). Later in the process (*gray hepatization*) this sharpness is blurred and lost owing to the action of proteolytic enzymes,

the red cells are mere ghosts, the threads of fibrin become clumped, and the pneumococci disappear. The polymorphonuclears are replaced by macrophages which are now the active cells (Robertson and Uhley). These appear to be derived from the lymphocytes and monocytes of the alveolar exudate (Loosli). On the other hand silver impregnation shows that the alveolar walls contain cells bearing a close resemblance to the microglia of the brain and the cells of the reticuloendothelial system (Marshall). At least some of the macrophages may arise from these cells. In the final stage known as *resolution* the softened exudate is completely removed, partly by coughing, partly by transportation by phagocytes to lymph nodes, and partly by solution and absorption. By these means the consolidated lung is rapidly restored to normal.



FIG. 204.—Lobar pneumonia, early stage. The alveoli, which are crowded with pneumococci, contain edema fluid but no leucocytes.  $\times 1300$ .

**THE RELATION OF SYMPTOMS TO LESIONS.**—The *physical signs* are easily explained by the pathological findings. The dulness, blowing breathing, increased vocal fremitus and resonance are caused by a conversion of the lung into a solid organ which conducts sounds from the large bronchi to the chest wall with the greatest readiness. The moist râles heard during resolution are caused by the liquefied exudate in the bronchioles. The *pain* is due to pleurisy. It is an early symptom, because the pneumococci reach the surface long before consolidation has become complete. The *sputum* is rusty in color because it contains broken-down red cells. If there is much alveolar hemorrhage the sputum will contain bright blood. The sputum is very tenacious and stringy owing to its highly fibrinous character. The *blood* shows a high leucocytosis owing to the extensive character of the leucocytic exudate. Blood culture may be positive, but it is a sign of ill-omen except in the

earliest stages. In cases which are going to recover the pneumococci usually soon disappear from the blood.

The *respiratory disturbances* (dyspnea, rapid shallow breathing, and in the more severe cases cyanosis) cannot be explained merely by the exudate in the lung, for they may be marked even though the pulmonary lesion is quite limited. They appear to be bound up with the condition of lowered oxygen saturation of the arterial blood known as *anoxemia*, the index of which is cyanosis. The means by which the anoxemia is produced is not certain.

**COMPLICATIONS.**—*Organization* of the inflammatory exudate may occasionally occur. It becomes changed from fibrin into fibrous tissue. The strange thing is that this does not happen more frequently. Usually resolution occurs in time and the exudate melts away before fibroblasts have time to invade it. When organization occurs fibroblasts grow into the exudate from certain points of the alveolar wall,

especially the angles, and these are soon followed by capillaries which later disappear. Long strands of fibrous tissue are formed which traverse the alveoli, often passing from one alveolus to another through what appear to be openings in the walls (Fig. 206). The end-result of these changes is to convert the lung into a dense elastic structure. As it is fleshy in consistence the process is known as *carnification*.

Pulmonary fibrosis secondary to pneumonia is seen more frequently than formerly. This may be attributed to two factors: the successful use of antibiotics and an increase in virus pneumonia (Auerback, *et al.*). Both the clinical and the pathological picture of pneumonia are undergoing a change.

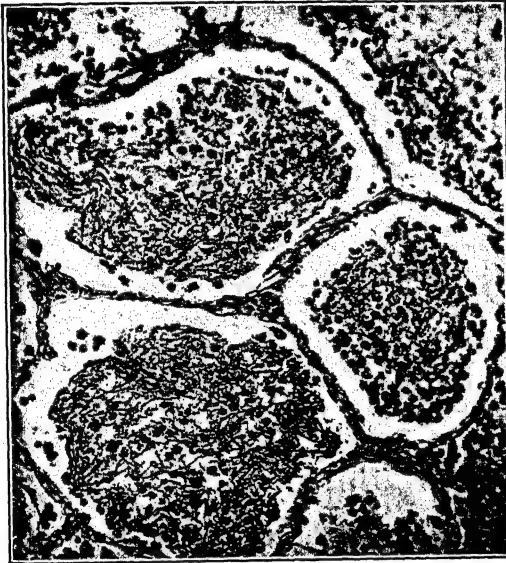


FIG. 205.—Lobar pneumonia. The alveoli are filled with an acute fibrinous exudate.  $\times 100$ .



FIG. 206.—Organization of a pneumonia exudate. A strand of fibrous tissue passes through an opening in the alveolar wall.  $\times 150$ .

*Suppuration and abscess formation* are not common, and are due either to a very virulent infection or to poor resistance on the part of the patient. The alveolar walls are broken down and the exudate becomes purulent. It must be understood that although the exudate in lobar pneumonia may consist largely of polymorphonuclear leucocytes, this is not pus, and, as a rule, there is no suppuration, *i.e.*, breaking-down of tissue. Empyema may develop, but this is not common except in children, though a frequent complication of streptococcal pneumonia. Spread of the infection may also cause pericarditis. As a result of pneumococcal septicemia there may be endocarditis, meningitis, and arthritis.

### BRONCHOPNEUMONIA

This condition, also called lobular pneumonia on account of its patchy character, is not a definite entity like lobar pneumonia. As a secondary



FIG. 207.—Streptococcal bronchopneumonia, showing patchy character of the exudate.  $\times 60$ .

condition complicating and often terminating other diseases it is extremely common. Indeed in hospital autopsies it is seldom that some degree of bronchopneumonia cannot be demonstrated. As a primary disease it occurs principally in childhood and old age. The susceptibility of the child may be due to poor expulsive power, to the delicate mucosa, or to the short wide bronchial tree. The pneumonias following measles, whooping cough and other infectious fevers are bronchopneumonic in type; so also are the postoperative and terminal pneumonias. It is usually due to streptococci, but pneumococci, staphylococci and influenza bacilli may be the predominant organisms.

There is a patchy consolidation of both lungs, a lobular pneumonia which can often be

felt better than seen. Sometimes the patches fuse together, giving a confluent bronchopneumonia which may simulate lobar pneumonia. Collapsed areas, dark purple in color and depressed below the surface, are seen on the outside of the lung especially in children. The collapse is caused by the bronchioles becoming filled with secretion, so that the air cannot enter the lobule; the imprisoned air in the alveoli is then absorbed and the lobule becomes collapsed. The collapsed areas are surrounded by emphysematous bullæ, a compensatory arrangement. A thin fibrinous exudate covers the surface. On the cut surface the patchy character of the lesions is very evident, areas of consolidation alternating

with areas of collapse, of emphysema and of normal lung tissue. The patchiness can be seen even better with the naked eye in a stained section. The consolidated areas are then seen to be grouped around small bronchioles. The bronchial lymph nodes are enlarged and soft.

*Microscopically* there is an intense inflammation of the bronchial wall, the lumen of which is filled with pus and desquamated epithelium. There is more of a bronchiolitis in streptococcal pneumonia than in the lobar form. The bronchiole is surrounded by a ring of alveoli filled with an inflammatory exudate consisting mainly of polymorphonuclear leucocytes with a moderate amount of fibrin (Fig. 207). Farther out the alveoli contain mononuclear cells and edematous fluid. The consolidated areas alternate with areas of congestion, collapse, and emphysema.

Recovery is often not complete. The walls of the bronchi are damaged, granulation tissue is formed followed by fibrosis, and permanent bronchiectasis may result. Moreover there is no distinct crisis, and absorption of the exudate tends to be delayed so that organization may occur. In these respects the disease differs from lobar pneumonia, which is a more satisfactory and honest type of infection and one easier to treat.

## INFLUENZAL PNEUMONIA

The general problem of influenza and the question of its bacteriology have already been discussed in Chapter 7. The conclusion arrived at there was that influenza is due to a filter-passing virus assisted by *Bacillus influenzae* and other organisms. One of the greatest difficulties is to distinguish between the lesions of a pure infection and those due to secondary invaders. The influenza virus lowers the resistance to such a degree that secondary infection (*influenza bacillus*, *streptococcus*, *pneumococcus*) occurs with great readiness. It is these invaders which produce the pneumonic consolidation, although certain fundamental features of the lesions, common to all the forms, may be attributed to the action of the virus.

**SYMPTOMS.**—The most characteristic symptoms of influenza are profound prostration, a dry hacking cough, and leucopenia in place of the usual leucocytosis of acute infections. In addition, in the more severe cases with pulmonary complications there may be cyanosis, dyspnea, watery blood-stained sputum, pleurisy, and not infrequently empyema.

**LESIONS.**—It is difficult to speak with confidence of the lesions of a pure influenzal infection, because the number of cases on record in which influenza virus has been demonstrated at autopsy and the pathological changes described is incredibly small, and in fewer still have there been no bacterial invaders. From the work of Parker and his associates the essential features appear to be hemorrhagic edema together with a small amount of fibrin in the alveolar spaces and the formation of a hyaline membrane lining the alveolar walls. The lesions, indeed, are minimal. The almost universal occurrence of secondary bacterial infection gives rise not only to pneumonia but also to the necrotizing bronchitis and bronchiolitis so frequently seen. The trachea and bronchi are intensely congested, and the ciliated epithelium is desquamated (Fig. 208), thus opening the way to secondary invaders. The alveolar walls are thickened and infiltrated with lymphocytes and mononuclear cells. The bronchioles are filled with pus, their walls are damaged, and there may be subsequent dilatation and bronchiectasis.

The pneumonic lung varies in appearance, but the lesions are constantly bilateral. At the height of an epidemic, and sometimes in sporadic cases, the lungs are voluminous, covered by a thin fibrinous exudate, and of a vivid red color with

splashes of a dusky purple. From the cut surface pours a bloody watery fluid due to a hemorrhagic edema which is the outstanding feature of the condition. In a marked case a correct diagnosis can be made at a glance. The lung is heavy, but without the firm consolidation of lobar pneumonia or the nodular consolidation of bronchopneumonia. The most marked feature of the microscopic picture is edema fluid filling the alveoli, with numerous red blood cells but few leucocytes and no fibrin. The alveoli may occasionally be lined by a hyaline membrane apparently derived from the albuminous fluid within the alveolar spaces. In interepidemic periods the picture is less dramatic, but hemorrhagic edema is still the characteristic lesion. At the beginning of an epidemic, before secondary invaders have attained a high virulence, a nodular peribronchial interstitial pneumonitis may be the dominant lesion. Inflammatory cells may fill the alveoli as well as bronchial wall and interstitial tissue, so that small nodular lesions are produced which may resemble miliary tubercles.



FIG. 208.—Trachea in influenza. Desquamation of epithelium, congestion of mucosa, and infiltration with inflammatory cells.  $\times 300$ .

**THE RELATION OF SYMPTOMS TO LESIONS.**—The dry, hacking cough is due to the acute tracheitis and bronchitis. Cyanosis and dyspnea are probably due to interference with the exchange of gases in the alveoli, this in turn being caused by the copious outpouring of fluid. The watery, frothy, hemorrhagic sputum merely represents an external appearance of the hemorrhagic edema of the lungs. The profound prostration, the most striking of all the symptoms of true influenza, is due to the general toxemia. So also is the Zenker degeneration of muscle and other changes of a general character which are not discussed in this place.

### OTHER FORMS OF PNEUMONIA

**Virus Pneumonia.**—Pneumonia, or rather pneumonitis, may occur in a number of virus diseases. The more important of these are influenza, psittacosis, Australian Q fever, and the so-called primary atypical pneu-



monia. The great difference between virus infections of the lung and bacterial pneumonias is that in the former the chief lesion is an interstitial inflammation, as evidenced by lymphocytic and mononuclear infiltration of the walls of the bronchioles and the lung framework with a varying degree of alveolar edema, whereas in the bacterial pneumonias the cellular and fibrinous exudate occupies the alveolar spaces.

*Primary atypical pneumonia*, often referred to specifically as virus pneumonitis, is a new arrival in the infectious field. The infection causes an acute inflammation of the mucous membranes of the upper respiratory tract, occasionally extending to the trachea and bronchi and in a few cases to the bronchioles and lungs. The morbidity is high, but the mortality low. The physical signs are largely negative, but there is roentgen-ray evidence of a patchy, ill-defined consolidation, seldom involving more than a portion of a lobe. The course is usually mild, lasting two or three weeks, and a fatal outcome is rare. Inoculation of all the laboratory animals proved negative, but Weir and Horsfall found that in the mongoose a pneumonia was produced which was bacteriologically sterile. This pulmonary lesion was marked by extensive edema of the alveoli and alveolar walls, together with small numbers of mononuclear cells. The virus is readily propagated on the chorio-allantoic membrane of the chick embryo. In new-born children a form of epidemic pneumonia has appeared which is apparently due to a virus. It is highly contagious, the mortality is high, and cytoplasmic inclusion bodies are present in the bronchial epithelium.

Robertson and Morle have challenged the concept that primary atypical pneumonia is a virus disease. They believe it to be a segmental aspiration pneumonia due to the aspiration of mucus or pus from the upper respiratory tract. They point out that the one constant radiological feature is anatomic localization to bronchopulmonary segments, with fan-like shadows in the middle and lower lobes, that identical lesions follow the aspiration of blood, that the illness begins as an upper respiratory infection, that symptoms often develop after severe physical exercise during such an infection with rapid or gasping breathing predisposing to aspiration, and that there is no real evidence in support of a specific pneumo-tropic virus.

*Psittacosis* (*psittakos*, parrot), is a virus pneumonitis of birds and man of high mortality, which is described on page 182.

*Q fever*, which derives its name from having been first described in Queensland, Australia, in 1937, is caused by a rickettsia, is carried by rodents, and is spread by ticks. The remarkable feature of the disease, which is widespread throughout the world, is the absence of any correlation between the pathological lesions in the lung and the clinical picture, which is that of a typhoid-like state. There is a definite pneumonitis, with soft patchy lesions in the x-ray film, but a complete absence of respiratory symptoms. Unlike psittacosis, the mortality is very low. The pathological lesions are similar to those of primary atypical pneumonia, namely mononuclear infiltration of the bronchial walls with edema and inflammatory cells in the lumen of the bronchi and alveoli.

**MUCOSAL RESPIRATORY SYNDROME.**—This descriptive term, suggested by Stanyon and Warner, has been applied to a condition characterized by inflammatory lesions of mucous membranes, skin and lung, and caused almost certainly by a virus. The condition is sometimes referred to as the Stevens-Johnson syndrome. The mucous membranes involved are those of the mouth, conjunctiva, and genital

tract. The onset and spread of the stomatitis is rapid and dramatic, and within a few hours the mouth is a mass of large, shallow, extremely painful ulcers. The lungs are consolidated by what is evidently a virus pneumonia, with great edema, an alveolar exudate consisting entirely of mononuclear cells, extreme swelling of the alveolar lining cells, loss of bronchial epithelium, and mononuclear infiltration of the bronchial walls. In some cases there are erythematous or hemorrhagic lesions of the skin.

**POSTOPERATIVE PNEUMONIA.**—*Aspiration pneumonia* is due to aspiration of septic material during an operation; there is more danger of this during general anesthesia, but it may occur under a local anesthetic. Operations on the mouth and tonsils are the chief danger. Suppuration and abscess formation are common. The bacteriology is naturally very varied. *Aspiration of stomach contents* as the result of terminal vomiting produces a characteristic postmortem picture. Both lungs are of a dirty dark color, of soft almost mushy consistence, and have a sour, acid smell. The condition is of course not pneumonia but postmortem digestion.

The work of Yandell Henderson, Coryllos, and others suggests that *atelectasis* may be an important factor in the production of postoperative pneumonia and possibly in other forms of pneumonia, especially in the new-born. When a patient lies on his back after a general anesthetic the bronchial tree tends to become filled with secretion so that the bronchioles are blocked. The free drainage by which the lung is kept in an aseptic condition is interfered with, the air distal to the obstruction is absorbed, the corresponding lobules collapse, and in the occluded area a mild pneumonia is likely to develop.

**TERMINAL PNEUMONIA.**—Pneumonia may be found at autopsy as a termination of a chronic illness in which there is no hint of fever to suggest a pneumonic process. The consolidation is usually patchy in character and basal in distribution, so that it is often called hypostatic pneumonia. Hemorrhage and edema (hypostatic congestion) are common terminal conditions in the dependent parts of the lung and are often associated with terminal pneumonia. The inflammation is a mild one, and is due to the growth of organisms of low virulence in devitalized tissues rather than to invasion by virulent organisms. The bacteriology is of a very mixed description. The alveoli are filled with mononuclear cells together with a few polymorphonuclears, red blood cells, and much edematous fluid. There is a notable absence of fibrin, nor is there usually any pleurisy (hence the absence of pain).

**STAPHYLOCOCCAL PNEUMONIA.**—This is an uncommon form of primary pneumonia. The onset is often abrupt with chills, high remittent fever, and signs and symptoms first of bronchopneumonia and later of lung abscess. The sputum is yellowish, highly purulent, odorless, and swarming with staphylococci. The lesions are bronchopneumonic, developing later into multiple abscesses. The disease may appear in epidemic form with a high mortality.

**PNEUMONIA IN THE NEW-BORN.**—Pneumonia is a common cause of stillbirth. The infection, acquired *in utero*, may be due to inhalation of amniotic fluid or may possibly be caused by maternal infection. Many stillborn children show evidence of aspiration of amniotic fluid without definite pneumonia. Farber points out that the most important contents of this fluid are cornified desquamated epithelial cells from the skin of the fetus and vernix caseosa which is rich in fat and fatty acids. In the alveoli the desquamated epidermal cells take the form of long wavy structures with pointed ends. The vernix caseosa is pressed tightly against the walls of the alveoli and bronchioles as the result of inspiratory efforts by the child, and resembles the inflammatory "hyaline membrane" of influenzal pneumonia which is formed from albuminous intrapulmonary fluid in very much the same way (Fig. 209). This vernix membrane stains red with eosin, and red with scarlet R. in frozen sections owing to its fatty nature.

**CHEMICAL PNEUMONIA.**—During World War I poison gas often produced acute pulmonary lesions much like those of influenzal pneumonia. There was the same acute hemorrhagic edema, and the patients were often literally drowned in their own fluids. If the patient recovered the lungs were permanently damaged and liable to recurring infections.

**LIPOID PNEUMONIA.**—This term denotes an inflammatory condition of the lung caused by the presence in the alveoli of animal or mineral oil. It may develop when the throat has been repeatedly sprayed with mineral oils, liquid petrolatum, etc., especially in children. The habitual forced administration of cod-liver oil in children is another cause. It is important to realize that light oils can pass with ease



FIG. 209.—Hyaline membrane in pneumonia of the new-born.  $\times 500$ .



FIG. 210.—Oil pneumonia; phagocytes filled with globules.  $\times 450$ .

from the upper respiratory passages to the lungs. The condition is much commoner than has been suspected, the incidence having increased greatly since the existence of the lesion was first demonstrated by Laughlen in 1925. This is due to the widespread habit of self-medication by the public who so frequently use oily sprays or drops for upper respiratory infections. Animal oils, particularly cod-liver oil, are highly irritating. Liquid petrolatum, although less acutely damaging, produces severe chronic effects, as it leads to the formation of reticulum fibers, giant cells, and finally extensive fibrosis. In the gross the affected areas are gray or yellow and moderately firm, projecting slightly above the pleural surface. The patches become firmer and grayish-white, and may be mistaken for tumor metastases. The alveoli are filled with large phagocytic cells (lipophages) distended with droplets of oil, giving a highly characteristic microscopic picture (Fig. 210). It must be pointed out that macrophages filled with lipid may be present in the alveoli apart from true lipoid pneumonia. They are seen in pulmonary tuberculosis, chronic suppuration, and in the vicinity of large infarcts. In such cases the lipid must be of endogenous rather than exogenous origin. It is possible that some of the fat has been transported from the liver, because much of the fat in a grossly fatty liver makes its way

into the veins. Liquid petrolatum stains with scarlet red but does not reduce osmic acid, whereas cod-liver oil reduces osmic acid, and the same is true of vegetable oils. In the later stages fibrosis is marked, and giant-cell formation is common. The disease occurs at the two ends of life, and the adult form is characterized by a dense fibrosis which is often so clearly localized that it may be mistaken for a neoplasm (paraffinoma of lung).

**LÖFFLER'S PNEUMONIA.**—The condition usually known as Löffler's syndrome, first described in 1932, is characterized by a mild clinical course, marked eosinophilia, and transitory pulmonary lesions which present a remarkable and alarming picture in the x-ray films. Little is known about the pathological lesions, because the patient seldom dies. In a careful study by Bayley, Lindberg and Baggenstoss, the following changes were observed. Scattered throughout the lungs were focal areas of consolidation. Some of these consisted of fibrous tissue with an intermingling of great numbers of eosinophilic leucocytes, whilst others presented a granulomatous picture with epithelioid cells, numerous eosinophils, and fibrinoid degeneration of collagen. Widespread vascular lesions were present, in particular a necrotizing arteritis similar to that seen in periarteritis nodosa. In the bronchi there was marked hypertrophy of the muscle and extensive eosinophilic infiltration, lesions identical with those of bronchial asthma. The entire picture is strongly suggestive of an allergic reaction. The allergic agent may not be the same in every instance. In some cases the larvae of *Ascaris lumbricoides* which migrate through the lungs may be responsible, whilst in others the antigen responsible may be pollen or bacteria.

**GIANT-CELL PNEUMONIA.**—This condition, first described by Hecht in 1910, is an interstitial pneumonitis of infants and young children characterized by the presence of large multinucleated giant cells. It has been suggested by Chown that it is a manifestation of vitamin A deficiency. Pinkerton and his associates describe cell inclusions, both cytoplasmic and intranuclear, in several cases, and point out the close resemblance of the lesions to those of dog distemper. For this reason they believe the condition to be due to infection by a virus, possibly closely related to that of distemper. It is possible that the cellular disturbance produced by the virus may render impossible adequate utilization of vitamin A.

**RADIATION PNEUMONITIS.**—When the chest is exposed to repeated doses of therapeutic radiation reactive changes may occur in the lungs. The alveolar lining cells enlarge, and some become very hypertrophic and bizarre-like tumor giant cells. The bronchial epithelium shows similar but less extreme changes. The elastic tissue is ruptured and reduplicated. The alveoli may be lined by a hyaline membrane similar to that seen in epidemic influenza and in the new-born. The triad of epithelial hyperplasia, changes in the elastic tissue, and hyaline membrane lining the alveoli is pathognomonic. Injury to the tissues may lead to infection followed by fibrosis.

**BRONCHIOLITIS FIBROSA OBLITERANS.**—This uncommon condition may be considered here, although it is not a true pneumonia. Bronchiolitis may be the result of the inhalation of irritating gases, may occur in the course of the infective fevers, or may be apparently idiopathic. The wall of the bronchiole may be extensively damaged, a fibrinous exudate forms in the necrotic wall and in the lumen; this becomes organized by fibroblasts and capillaries, so that first granulation tissue and later dense connective tissue replace the bronchiole and its lumen. The alveoli are collapsed and may be involved in the fibrosis. The gross appearance of obliterating bronchiolitis is that of numerous miliary nodules scattered through the lung. The clinical picture is what might be expected: an acute phase with marked dyspnea and cyanosis; a short intermission; a final return of the dyspnea and cyanosis in either an acute or a more slowly progressing form.

## THE PNEUMOCONIOSES

The long-continued inhalation of certain irritating dusts may cause a chronic interstitial pneumonia known as pneumoconiosis (*konis*, dust). The outcome of these dust diseases is entirely dependent on the presence and amount of silica in the dust. The dangerous pneumoconioses are silicosis and asbestosis, both of which may be disabling or fatal. Anthracosis, a condition caused by the inhalation of carbon in coal dust, is harmless in comparison.

**Silicosis.**—Silicosis is the most widespread, the most serious, and the oldest of all occupational diseases. Silicon (Si) is the most widely distributed element in nature. The silicates merely give rise to a foreign body reaction, but silica ( $\text{SiO}_2$ ), like asbestos, causes a progressive productive reaction ending in fibrosis and associated with marked impairment of pulmonary function. This condition, known as silicosis, is the most important of the dust diseases, and provides a serious hazard in the gold-mining industry in certain districts such as the South African Rand and northern Ontario. The worker is in great danger, but men mining any type of ore are liable to develop silicosis. If, in coal mining, hard rock has to be drilled through, coal miners may also suffer. Other occupations in which there is danger are tin-mining, stone-working, metal-grinding and sand-blasting. In all of these cases dust containing fine particles of silica may be inhaled over long periods of time.



FIG. 211.—Fetalization of alveolar lining.  
× 160.

The particles of silica are taken up from the bronchioles, the epithelium of which is not ciliated, by phagocytes which carry them to the tiny lymphoid aggregations in the alveolar septa. The cell containing the silica undergoes changes similar to those seen in tuberculosis. The cytoplasm increases in amount and comes to contain lipoid droplets, whilst the nucleus may divide repeatedly, so that a typical Langhans giant cell may be formed. When silica is injected subcutaneously it produces necrosis, and the slow reaction in the lung results partly in necrosis but to a much greater degree in fibrosis. Both the rate and the extent of the fibrosis are in inverse proportion to the size of the silica particles. Previous disease processes, such as pneumonia, which may cause scarring of the delicate alveolar walls

and lymphoid collections will facilitate the arrest of the particles and predispose to the production of silicosis. In this and in other fibroid conditions of the lung the alveolar lining cells become cuboidal so that the alveoli assume a gland-like appearance like that of the early fetal lung, and the condition is, therefore, known as fetalization of the alveolar lining (Fig. 211). This transformation is probably due to loss of respiratory function. The basic process is proliferation of reticular fibers, which later become transformed into collagen. The elastic fibers disappear completely. The fibrosis is at first patchy, corresponding to the deposits of silica in minute lymph follicles adjacent to the terminal bronchioles, and takes the form of "silicotic nodules" (Fig. 212), composed of concentric layers of fibrous tissue



FIG. 212.—Silicosis showing characteristic fibrous nodules.  $\times 13$ .

and readily palpated in the lung. These nodules gradually coalesce, and the fibrosis becomes widespread. In extreme cases the lung becomes stony hard, and in one instance I had to saw the lung in two. When the lesions are produced by pure silica dust, as in gold miners and sand blasters, the nodules have the clean-cut laminated, onion-like character described above. When, however, as is frequently the case, the silica is mixed with other dusts, as in granite workers and anthracite coal miners, an interstitial fibrosis is added, and tongue-like projections extend from the nodules into the surrounding tissue. Moreover dust inclusions are commonly seen when the lesion is due to mixed dusts; these are seldom present in cases of pure silicosis. Emphysema is a common consequence of the extensive fibrosis, most marked, as a rule, at the base. The lymph nodes at the root of the lung are small, hard and fibrosed, with fibroblasts arranged in a characteristically whorled manner. The pleura is thickened and adhesions are common, due to deposits of silica in the subpleural lymphatics. The functional capacity of the lungs is greatly interfered with, and the chief

symptom is marked dyspnea. The necrotizing action of the silica may lead to destruction and cavitation, but these changes are usually due to an accompanying tuberculosis.

Most silicotics die of tuberculosis because the presence of silica in the tissues favors the growth of tubercle bacilli to an astonishing degree. The lesions of silicosis and tuberculosis are at bottom essentially similar. As Gardner remarks, it is strange that a simple inorganic compound like silicon dioxide can give rise to the same cellular reactions as the tubercle bacillus with its proteins, carbohydrates and lipids.

The *radiological appearance* is of great importance, because it forms the basis for the clinical diagnosis. The earliest change is an increase in the normal reticulation of the lung. The specific appearance, however, is that of clean-cut nodules scattered widely throughout both lungs, but in cases due to mixed dusts the outline of the nodules is much more hazy. When calcium is deposited in the nodules they stand out still more sharply. When tuberculous infection is added the nodules develop a fluffy outline, increase in size, and eventually coalesce to form large shadows; this is in contrast to pure silicotic lesions which may remain discrete for years.

Silicotic lesions are not confined to the lung. Silica may occasionally be carried to the liver and spleen, where it causes necrosis and fibrosis (Lynch).

**ANTHRACOSIS.**—A varying amount of coal dust is found in every lung at autopsy, and is usually of no significance. By itself coal dust appears to produce no harmful effect. In coal miners, however, it may give rise to the form of pneumoconiosis known as anthracosis. It does so because of the admixture of a certain amount of silica. In this mixed form the characteristic lesion is *dust-reticulation* (Belt), with corresponding fine net-like shadows (reticulation) in the roentgen-ray picture. Dust-reticulation is scattered diffusely throughout the lungs, forming a lace-like pattern along the lymphatic pathways and depots in which dust-laden macrophages are entrapped. The appearance of innumerable dust-ridden cobwebs is due to the formation of fine argentophil reticulum fibers; there is none of the collagen formation so characteristic of pure silicosis. The bronchial lymph nodes are masses of coal dust. In more advanced cases, which may be termed anthraco-silicosis, there may be *nodulation*, the formation of tiny nodules from 2 to 5 mm. in diameter. Finally there may be *confluent fibrosis*, a patchy confluence of the previous lesions. All of these features are due to the presence of the silica rather than the coal dust. Emphysema may be marked, due perhaps to destruction of the elastic tissue. Belt remarks that the collier's lung is in a very real sense his occupational log book; it retains a qualitative and an indelible record of the mineral particles breathed during life.

**PULMONARY ASBESTOSIS.**—This condition is due to the inhalation of asbestos dust which may contain over 50 per cent of silica. The disease is acquired either during the crushing of asbestos rock or in the process of carding the asbestos. The lung shows the airless and fibrosed condition found in silicosis, and on the cut surface there are areas of caseation with cavity formation. The characteristic microscopic feature, in addition to a large amount of silica dust, is the presence of large angular particles which are probably fragments of asbestos fibers, and curious golden-yellow bodies with a globular end and segmented body (Fig. 213.) The latter structures, which may be called asbestos bodies, are pathognomonic of the condition, but their exact nature is not understood.



**BERYLLIUM PNEUMONITIS.**—A modern industrial hazard is the pneumonitis produced by beryllium, used principally in the manufacture of fluorescent lamps and also in other industries. The illness may be acute, with recovery when the worker is removed from exposure to the irritant. More important is delayed beryllium poisoning, the symptoms appearing months or a year or two after exposure. The lesions take the form of granulomatous nodules, and resemble those of sarcoidosis. Conchoidal bodies similar to those seen in sarcoidosis are often present either in the giant cells or the granuloma. The hilar nodes are also involved. The end stage is extensive fibrosis, causing severe dyspnea and eventually right heart failure. The incidence among workers in a plant is low, the distribution spotty, and there is lack of relationship between the severity of the disease and the degree of exposure. Direct and obvious exposure is apparently not necessary, for persons living near a beryllium plant but not working in it have developed the chronic pulmonary form of the disease (Chesner).



FIG. 213.—Asbestos body showing globular ends and segmented appearance. (Specimen of Dr. J. E. Pritchard.)



FIG. 214.—Bauxite fibrosis.  $\times 210$ .  
(Kindness of Dr. J. P. Wyatt.)

**BAUXITE FIBROSIS.**—Quite different from the other pneumoconioses are the lesions produced by the dust of bauxite, an alumina abrasive. There is a diffuse reticulated fibrosis with none of the nodularity so characteristic of silicosis (Fig. 214). Large emphysematous bullæ form a striking feature, and pneumothorax is a common consequence. Dyspnea is extreme, and the progress is rapid and fatal.

**GRAPHITE PNEUMOCONIOSIS.**—Graphite or plumbago is a crystalline form of carbon which is extensively used in the manufacture of lubricants, electric batteries, lead pencils, etc. Persons engaged in mining or grinding graphite appear to be exposed to the greatest dust hazard. The lung shows a granulomatous reaction, with areas of fibrosis, necrosis and caseation. Asteroid inclusions may be present in the numerous giant cells (Jaffe).



**PULMONARY FIBROSIS OF UNCERTAIN NATURE.**—Occasional cases are encountered by every pathologist in which there is more or less extensive interstitial fibrosis without any satisfactory explanation. They may be associated with a marked degree of compensatory emphysema. Some of these cases may represent healed disseminated miliary tuberculosis infected from an extra-pulmonary source. In others there may have been a previous virus infection which damaged the pulmonary framework. Hamman and Rich report 4 cases of *acute* interstitial fibrosis of the lungs in which the pathological process was evidently rapid with accompanying right-sided heart failure. Belt describes fatal pulmonary fibrosis due to industrial exposure to radium over a period of two years. It is probable that there are other still unsuspected etiological agents. In my own experience one of the important conditions which may be responsible for what has been well named idiopathic pulmonary fibrosis is sarcoidosis, which may give rise to extensive, disabling and finally fatal fibrosis. Sarcoidosis may be overlooked. Lymphatic obstruction, whether due to inflammation or tumor, may be followed by extensive fibrosis. A long list of causes of pulmonary fibrosis will be found in Mallory's excellent paper, but there still remains the occasional "idiopathic" case of uncertain nature to puzzle the pathologist.

## SUPPURATIVE CONDITIONS OF THE LUNG

Septic diseases form along with the pneumonias and tuberculosis the great trio of pulmonary infections. Many cases of supposed tuberculosis in which tubercle bacilli can never be found in the sputum belong to this group. The use of the bronchoscope and of lipiodol in the investigation of the bronchial tree has served as a great stimulus to the study of these diseases. The chief of these septic or suppurative conditions are abscess, gangrene, and bronchiectasis.

**Abscess and Gangrene.**—There is no sharp line to be drawn between abscess and gangrene of the lung. The former is a suppurative condition more or less circumscribed, while the latter is putrefactive and tends to be diffuse.

**ETIOLOGY.**—The cases may be divided into three groups: the inhalation, the embolic, and the pneumonic, depending on the method of causation.

1. The *inhalation group* is far the largest and most important. Abscess of the lung is a constant threat in operations on the mouth, nose, and throat. Tonsillectomy being the commonest operation is most often complicated by pulmonary sepsis, but this may happen with the removal of adenoids, operations on the nose, and the removal of teeth, and it may follow a local as well as a general anesthetic. The chief feature of the bacteriology of the inhalation group is its mixed character. This is in contrast to embolic abscesses or those due to staphylococcal pneumonia in which cases there is often only one infecting organism. The abscess is commoner in the right lung, perhaps because this lung has a more vertical bronchus. Foreign bodies may pass down the bronchial tree and give rise to abscess formation, especially in children. Septic material from the nasal sinuses, food regurgitated during general anesthesia, etc., may pass down the bronchial tree and cause an abscess. These foreign body abscesses must be distinguished sharply from other forms, because if the foreign body can be removed by means of the bronchoscope the prognosis is remarkably favorable. A metallic foreign body tends to cause hyperplasia rather than liquefaction

of tissue, and when it is removed a complete cure may result. 2. The *embolic group* is caused by particles of a septic thrombus being carried to the lungs. As these particles are numerous the abscesses are nearly always multiple. 3. The *pneumonic group* is usually streptococcal. In lobar (pneumococcal) pneumonia it is very rare for the consolidated area to develop into an abscess.

There remains a miscellaneous group where infection may spread from a neighboring organ, *e. g.*, the esophagus, the vertebral column, or from below the diaphragm. Bronchiectatic abscesses form a group which will be considered separately.

**SYMPTOMS.**—The chief clinical manifestations of abscess of the lung are (1) cough and copious expectoration of pus, (2) foul breath and sputum, (3) elastic tissue in the sputum, (4) dulness on percussion. The signs of gangrene are the same as those of abscess, and often the two conditions are combined.

**LESIONS.**—Abscess is commoner in the right lung, and is as frequent in the upper lobe as in the lower. The lesion is at first a solid mass of yellow inflammatory tissue, but as liquefaction occurs a cavity is formed filled with pus. This cavity may be of any size, from the smallest to the largest. The wall is ragged and necrotic, but in the more chronic forms a wall of fibrous tissue is built up and the lining becomes smooth. Owing to the close relationship in the pulmonary lobule between the bronchus and blood-vessels thrombosis is frequent, and this leads to extensive necrosis. The abscess is usually single at first, but secondary abscesses may occur at any time due to aspiration of infected material into other segments. The inhalation abscess is likely to communicate with a bronchus, the embolic abscess is not. Because the abscess is in the periphery of the lung the communicating bronchus is always small, rarely exceeding 2 to 3 mm. in diameter. A chronic abscess may show epithelialization of its wall from the bronchus. The *microscopic appearance* is that of an acute abscess with dense infiltration of polymorphonuclear leucocytes and a varying number of mononuclear phagocytes. The alveolar walls are destroyed, whereas in pneumonia they are preserved. As the condition becomes chronic fibroblasts multiply, and a wall of fibrous tissue is built up around the abscess.

The *odor* of the contents depends largely on whether the lesion is a suppurative or a gangrenous one. In an abscess uncomplicated by gangrene the contents may be inoffensive, but when gangrene supervenes the smell is horrible. This is due to decomposition of the proteins by saprophytes, of which the most abundant are *spirochetes* and *fusiform bacilli*, which are found in the contents of the cavity, in the sputum, and in sections of the lung. They are largely responsible for the necrosis. These organisms are secondary invaders from the mouth, where they occur in connection with carious teeth and pyorrhea.

*Gangrene* may be preceded by abscess formation or may be the primary condition owing to the aspiration of heavily infected material. In debilitated persons a pneumonia may become gangrenous. Soft green areas are formed, and these break down with the production of ragged cavities filled with foul-smelling stuff. Blood-vessels traversing the cavity may be opened, sometimes with fatal hemorrhage. Gangrene of the lung is likely to be rapidly fatal.

**THE RELATION OF SYMPTOMS TO LESIONS.**—Pus may be expectorated in large amount, but this depends on whether the abscess communicates with a bronchus. Such a communication exists in bronchiectasis, in an inhalation abscess, and when an abscess bursts into a bronchus. If the abscess can be drained by means of the bronchoscope or even by effective coughing it may become healed. In an embolic abscess there is no communication with a bronchus, so that no pus is expectorated. The *sputum* may be very characteristic, thick, purulent, yellowish-green in color, and often very abundant. *Elastic tissue* in the sputum indicates destruction of the lung. *Pleurisy* is common, because the abscess is often subpleural in position. *Empyema* may be caused by rupture of the abscess into the pleural cavity. *Brain abscess* is a common complication due to septic embolism. Two curious points should be noted: (1) that the cerebral abscess is often single, and (2) the nearly invariable absence of abscesses in the other organs. It is probable that the route of infection is by the vertebral series of veins described by Batson and others.

**Bronchiectasis.**—A dilatation of the bronchi, either local or general is known as bronchiectasis. Stagnation of the bronchial contents follows the dilatation, with resulting infection and suppuration. Minor degrees of the condition are common, although often missed clinically unless lipiodol is used.

**ETIOLOGY.**—The two main factors are infection and bronchial obstruction. The *infection* causes chronic inflammation of the bronchial walls with destruction of the musculo-elastic tissue resulting in dilatation of the part of the bronchial tree whose walls are damaged; the pathogenesis is the same as that of aortic aneurism. The dilatation favors accumulation of secretion with added infection and further injury to the bronchial wall. There may be a physiological block due to paralysis of the cilia from infection or metaplasia of the columnar epithelium into a squamous type, thus interfering with the normal mechanism for the removal of secretion (Robinson). A marked obliterating endarteritis may still further lower the resistance of the bronchial walls. In young children the process tends to be more acute, so that the first lesion is an ulcerative bronchitis with secondary destruction of the bronchial wall (Erb).

The acute infection, commonly occurring in childhood, may be measles or whooping cough, and occasionally influenza or pneumonia. The actual onset of symptoms is insidious, and is not ushered in by any acute illness. Neither gross upper respiratory tract infection nor chronic bronchitis is a common cause of bronchiectasis. Spirilla and fusiform bacilli are frequently found in the walls of the dilated bronchi, but it seems more probable that these are secondary invaders than primary etiological agents.

*Obstruction* of the bronchi leads to accumulation and stagnation of secretion, infection and weakening of the bronchial wall. The obstruction may be due to carcinoma, a foreign body, or pressure from without by aneurism, etc.

The pathogenesis of bronchiectasis is more involved, obscure and controversial than the foregoing account would indicate. As Mallory points out, a single agent is seldom sufficient to produce the condition. In his opinion bronchial inflammation in combination with atelectasis or pneumonitis will account for most of the features of the disease.

**LESIONS.**—Bronchiectasis may be diffuse (cylindrical form) or localized (saccular form). The former is the more common (Fig. 215). It is

usually bilateral, but it is rather remarkable that quite often it is unilateral. For some unknown reason the left lung is more often involved than the right, and the lower lobes more often than the upper owing to stasis. Only one lobe may be affected. The size of the cavity depends on the size of the bronchus. It is filled with pus which stagnates there owing to insufficient drainage, and still further weakens the wall of the bronchus. The mucosa is hypertrophic and may form tumor-like, highly vascular papillary masses. Later there may be atrophy. The *microscopic appearance* is similar to that of chronic abscess. The wall of the bronchus and the surrounding tissue

is infiltrated with chronic inflammatory cells. The mucosa may be hypertrophic or atrophic, and in advanced cases the muscle, glands, elastic tissue, and even the cartilage may be replaced by fibrous tissue (Fig. 216). The most significant lesion is the destruction of the bronchial musculature and elastic tissue, for it is these which weaken the wall and allow the dilatation to occur. Septic thrombosis may occur with embolism and the formation of a secondary brain abscess.



FIG. 215. — Bronchiectasis. The bronchi show marked cylindrical dilatation.

Liebow and his associates have shown by preparing casts of the vessels by the vinylite corrosion technic that a remarkable enlargement of the bronchial arteries occurs and that a rich anastomosis with the pulmonary arteries develops. So great is this enlargement and anastomosis that they estimate that more than a liter of blood per minute flows through this collateral circulation, which may well have some physiological importance for it tends to produce pulmonary hypertension.

#### THE RELATION OF SYMPTOMS TO LESIONS.

—The chief symptom is due to the chief lesion, the patient bringing up large quantities of *pus* at infrequent intervals, often when he

changes position (postural coughing due to the pus coming in contact with a new and more sensitive part of the bronchial wall) or on awakening in the morning. During the intervals the pus is accumulating. The character of the pus has already been described in connection with Abscess. *Hemorrhage* (*hemoptysis*) is common, occurring in 50 per cent of the cases, and is due to the highly vascular papillary masses of mucosa which may line the cavity or to erosion of vessels passing through the cavity. *Lipiodol* introduced into the bronchial tree outlines with beautiful distinctness the bronchial dilatations in a roentgen-ray picture, and has served to show the bronchiectatic nature of many cases of supposed tuberculosis and chronic bronchitis.

**CONGENITAL BRONCHIECTASIS.**—This rare condition is often called *congenital cystic lung*. It occurs in children. The lung is occupied by cysts of varying size lined by epithelium which may be cubical and ciliated or flattened. The condition is probably a congenital dilatation of the small bronchioles. The bronchi develop

as mesodermal buds which become canalized. If canalization does not occur at some point, but does occur distal to that point, an isolated segment will be formed lined by bronchial epithelium which secretes fluid and forms a cyst. The cyst may be single or multiple, small or large. The child suffers from severe attacks of dyspnea and cyanosis due to rupture of a superficial cavity and the production of a spontaneous pneumothorax. One of these attacks is likely to be fatal.

**INTRALOBAR SEQUESTRATION.**—This is a complex developmental anomaly consisting of two elements: (1) an anomalous artery, often of considerable size, an elastic pulmonary artery and not a muscular bronchial one, which arises from the aorta close to the diaphragm and enters the base of the lung; (2) a sequestered or

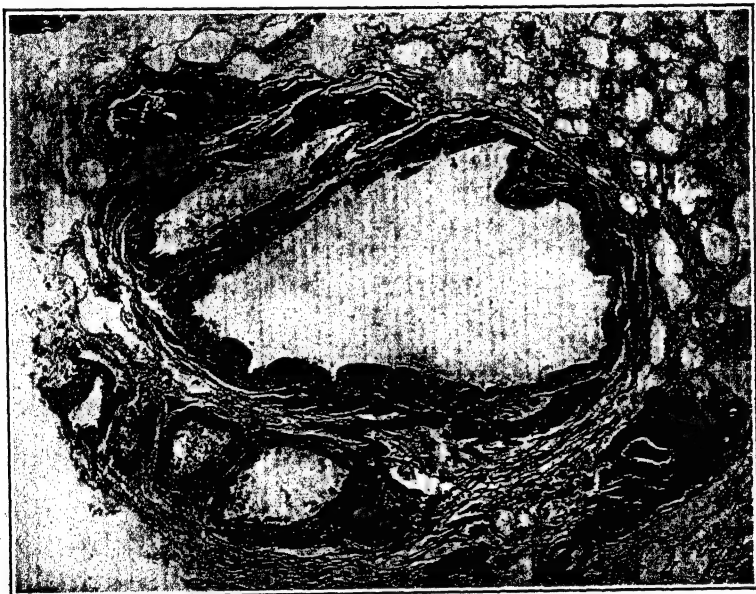


FIG. 216.—Bronchiectasis. Several small bronchi are dilated; their walls show fibrous thickening.  $\times 12$ .

dislocated mass of lung supplied by the abnormal vessel. The sequestered mass, which usually does not communicate with the normal bronchial tree, may take the form of a large cyst, or an area of polycystic lung connected with a blind bronchus, or a fibrosed mass of lung traversed by bronchi parallel with the abnormal artery (Pryce, *et al.*). Symptoms are mainly those of infection, and the condition is likely to be mistaken before operation for bronchiectasis, cystic lung, or empyema. The basal x-ray shadow may be triangular or round like that of a tumor.

## TUBERCULOSIS OF THE LUNGS

The general problem of tuberculosis has already been discussed in Chapter 7, and in order to avoid needless repetition the reader is referred to that account for a consideration of such questions as the method of infection, primary and secondary infection, the relation of the type of lesion to the age of the patient, etc. Some of the conclusions will be briefly summarized here.

Tuberculosis of the lungs is the commonest of all forms of tuberculosis, partly because by whatever route the bacilli enter the body they pass *via* the lymphatics to the venous blood stream and thus reach the lungs, partly because the lungs are especially exposed to direct infection. In the adult the infection is acquired by inhalation. The inhaled material may be infected dust or infected droplets of sputum. Children may place infected material in the mouth and this may be inhaled into the bronchioles and alveoli. The disease is now being seen more often in old people than formerly. At least that is true of British Columbia and Alberta in Canada.

The *incubation period* in so chronic a disease as pulmonary tuberculosis is difficult to determine, but it may be much shorter than anticipated as the following case in my own experience illustrates. A young man's tuberculin test was negative on June 25th. On July 12th he commenced animal experiments involving the use of living tubercle bacilli. On August 8th he developed general symptoms suggestive of infection and slight pain in the chest on breathing. On August 24th the tuberculin test was positive, on September 4th the roentgen-ray film was positive, and on October 17th the sputum contained tubercle bacilli.

Infection may *spread* from the original focus by the lymphatics, air passages, and blood stream.

1. *Lymphatic spread* is of special importance in the primary form. The lymphatics are perivascular and peribronchial and so are the lesions, which form a staphyloid group of tubercles around a central artery or bronchus. Such groups are often seen in the neighborhood of a caseous area. One of the tubercles may break through the wall of the bronchus or artery and rupture into its lumen causing a bronchial or blood spread of the infection.

2. *Bronchial spread* may occur when a focus opens into a bronchus (Fig. 217), and during the later stages infected material must be continually inhaled from one part of the lung to another, setting up fresh areas of broncho-pneumonia. The massive forms of tuberculosis such as tuberculous caseous pneumonia are mainly due to this bronchogenic spread.

3. *Hematogenous spread* is caused by rupture of a focus into a blood-vessel, usually a vein. This may cause miliary tuberculosis of the lungs as well as throughout the rest of the body.

The question of primary and secondary infection (reinfection) and the relation of age to the type of lesion are closely connected. It is customary to speak of the childhood and adult types of infection, but it is time that these terms are given up. The primary complex, *i. e.*, the reaction in tissues not sensitized to tuberculo-protein, used to develop in nearly every child, but now in many places not more than 10 or 15 per cent of children develop the infection, as shown by the tuberculin test. More primary infection now develops in adults than in children, and it is equally harmless in the great majority of cases. Primary infection is characterized by the Ghon lesion, seen in its active form in the child, in its healed (calcified) form in the adult. The secondary lesions of reinfection show a great variety of types, depending on the size of dose and the degree to which allergy or immunity happens to dominate the picture. The distinction between these

two processes has already been insisted on in the general discussion of tuberculosis.

**SYMPTOMS.**—The symptoms of pulmonary tuberculosis are both general and local. The chief *general* symptoms are fever, loss of weight, asthenia, night sweats, and anemia. Among the *local* symptoms are cough, expectoration, hemoptysis (spitting of blood), and pain in the side. There are *physical signs* of consolidation of the lung and cavity formation.

**A. Primary Infection.**—The primary lesion is a small caseous focus, seldom more than 1 cm. in diameter, usually though not always single, and situated in any part of the lung. In this it contrasts sharply with

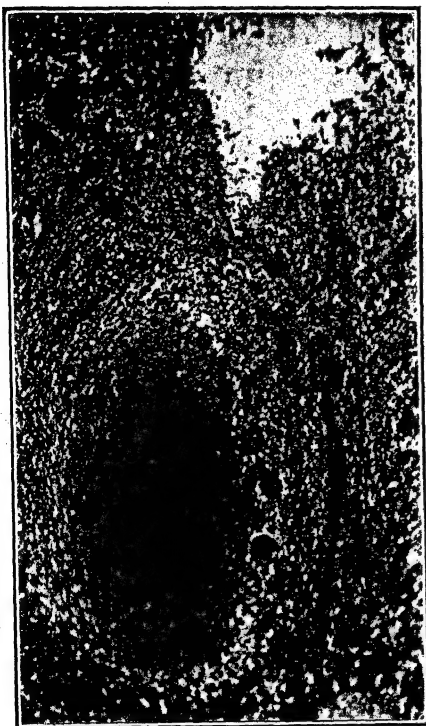


FIG. 217

FIG. 217.—Tubercle rupturing into a bronchus.  $\times 65$ .



FIG. 218

FIG. 218.—Active Ghon lesion. There is a subpleural caseous lesion in the lower lobe. The lymph nodes at the hilus are enlarged and caseous. Miliary tubercles are scattered through the lung, especially in the lower lobe. Some of the upper lobe has been removed. Death was due to general miliary tuberculosis.

the secondary lesion which nearly always makes its first appearance at the apex. The primary lesion may be in the lower lobe and is often at the periphery of the lung (Fig. 218). The caseous center becomes surrounded with a fibrous capsule. Calcification and sometimes ossification occur, and the healed lesion is represented by a small scar or calcified nodule. Foci in the regional lymph nodes also become encapsulated and calcified, but some caseous material usually persists and may harbor viable tubercle



bacilli for many years. Spread occurs primarily along the lymphatics, so that the regional lymph nodes are enlarged and caseous, again in contrast to what is found in secondary lesions. A chain of tubercles can be traced from the primary lesion to the infected lymph nodes. One of the caseous nodes may open into a bloodvessel and cause general miliary tuberculosis.

The patient with primary infection either recovers or dies; the disease does not become chronic, nor is there any cavity formation. If recovery takes place there is healing of the pulmonary and the glandular lesions by encapsulation with subsequent calcification. These healed primary lesions are most readily detected at autopsy by taking roentgen-ray pictures of the lungs, but calcified subpleural nodules may also be felt. Sometimes actual bone is formed in the primary lesion. The results of healing are: (1) calcified parenchymal and lymph node foci; (2) a state of allergy shown by the tuberculin test. About one-half of the population of the United States is tuberculin-positive. If healing fails to occur there may be general blood infection (miliary tuberculosis) or invasion of a bronchus with rapidly fatal bronchopneumonia. The course of the disease depends on such factors as size of dose and protection against frequent reinfection.

*Epituberculosis* is a clinical term applied to certain tuberculin-positive children who develop a characteristic wedge-shaped x-ray shadow with the base at the pleura and the apex at the hilus that appears suddenly or slowly and then gradually disappears. Although the lesion may be extensive, the symptoms are remarkably mild, and the child may feel perfectly well. The condition is therefore usually discovered accidentally. It appears to be a form of absorption collapse due to bronchial obstruction caused by pressure upon the wall by enlarged tuberculous lymph nodes. These may merely constrict the lumen or may rupture into the interior with the formation of tuberculous granulations (Hutchison). A similar shadow can be produced experimentally by injecting dead tubercle bacilli into the bronchial tree of an allergic animal; this causes a tuberculous pneumonia which clears by resolution. Human epituberculosis is probably a similar type of mild pneumonitis caused by a caseous node discharging into a bronchus a mass of tuberculo-protein and dead bacilli together with a few viable bacilli.

**B. Reinfection.**—This is usually an infection from without (exogenous), but it is probable that endogenous infection may occur from a primary lesion which has failed to heal. There is a curious immunity between the ages of five and fifteen, and death from pulmonary tuberculosis during these years is extremely rare. The reaction of the now allergic tissues is quite different from that of the primary infection. The right lung is attacked much more often than the left, and the lesion is nearly always just below the apex.

This remarkable apical localization is characteristic of secondary as opposed to primary infection. All sorts of fanciful explanations have been offered, but the most satisfying and that which agrees best with observed facts is the one offered by Dock, which is based on the low pulmonary arterial pressure at the apex owing to the height of the column of blood from the right ventricle to the apex when the patient is erect. It is now known that the pressure at the apex is practically nil when an adult is in the erect posture. In tall, long-chested persons, notoriously susceptible to tuberculosis, the mean pressure will be negative. As a consequence there will be no production of tissue fluid or lymph in the erect posture, immune bodies will not



reach the part, removal of oxygen from the alveoli will be minimal, and tubercle bacilli reaching the part will find optimum conditions for growth. Patients with mitral stenosis are almost immune from apical tuberculosis, and in them the pulmonary arterial pressure is sufficiently high to supply the needs of the part. On the other hand the disease is remarkably common in congenital stenosis of the pulmonary valve, a condition which produces the lowest known pulmonary arterial pressure. The higher incidence of right-sided apical lesions can be explained by the fact that the right pulmonary artery is longer and narrower than the left, winds around the aorta, and breaks into lobar branches at some distance before reaching the hilum of the lung. When ulceration or intense peribronchial inflammation occurs there is extensive hyperplasia of the bronchial arterial system with its high systemic blood-pressure, so that conditions become favorable for healing. These considerations explain and emphasize the importance of rest in the recumbent posture in the treatment of pulmonary tuberculosis. As Dock puts it, "it is the erect posture, maintained for many consecutive hours, which has given man an 'Achilles heel' through which the acid-fast arrow may pass." In other parts of the lung and in other organs an abundant blood supply under adequate pressure is an essential factor in the acquired immunity of civilized man to the tubercle bacillus.

The *result* will depend on the size of dose and the degree of resistance. If the dose is small and the resistance high there will be complete healing or a quiet fibrocaseous lesion at the apex. If resistance is not so good there may be rapid excavation, and as the result of cavity formation bronchogenic spread may readily occur. At this stage spread by the lymph stream and blood is comparatively rare, so that lesions in lymph nodes are insignificant. If the dose is large and resistance low there will be a widespread tuberculous caseous pneumonia with fatal termination. If a massive dose is discharged from a caseous gland into the blood stream there will be a general miliary tuberculosis.

The principal distinctions between the primary and secondary infections are the lack of any constant site in the primary form, caseous involvement of the lymph nodes, and the absence of liquefaction and cavity formation.

1. **HEALING WITH FIBROSIS.**—This is by far the commonest course for the infection to run. The lesion is usually at or just below the apex and takes the form of a small depressed pigmented scar which can often be better felt than seen, and is frequently adherent to the chest wall. The black pigment consists of carbon particles contained within phagocytes which have been arrested because of the blockage of the lymphatics by fibrosis. Lime salts are usually present, and are seen in the *x-ray* film.

In the past all *apical scars* have been considered either tuberculous or silicotic in nature. There is a third type which is much the commonest, and which Mac-Millan, working in my department in Toronto, found to be characterized by retention of the alveolar pattern. They have a constant structure by which they can be distinguished from the two other types, and seem to be the result of organized pneumonia, perhaps viral in nature. Medlar also came to the conclusion that the great majority of apical scars are non-tuberculous.

2. **CHRONIC FIBROCASEOUS TUBERCULOSIS.**—The characteristic reaction of a body already infected with tuberculosis to an additional heavy dose is breaking-down of the caseous tissue and the formation of a cavity. This is evidence of an allergic condition of the tissues, and is in no way connected

with immunity. The softened tissue is discharged into a bronchus and coughed up in the sputum. When the disease has reached this stage it is called "open tuberculosis," and tubercle bacilli are found in the sputum. The bronchial wall is involved in the softening and undergoes dilatation, so that the cavity is formed partly as the result of caseation and softening, partly as the result of bronchiectasis. The first cavities are formed at the apex, and these are always the largest, but as the disease progresses other cavities may be formed in the lower lobe. The formation of a cavity is due to the elastic outward pull on an area of softening; this explains its regular outline in the roentgenogram and its comparatively sudden development. The wall of the cavity is smooth, quite unlike the ragged lining of an acute

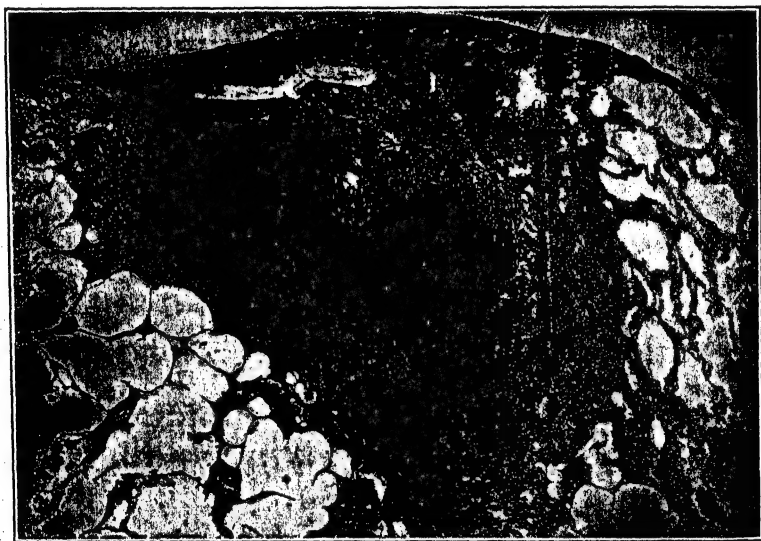


FIG. 219.—A healed tuberculous nodule in the lung.

cavity. It may be traversed by bronchi and bloodvessels, and erosion of the latter may lead to serious or even fatal hemorrhage (hemoptysis). In addition to the main areas of caseation and cavitation there are small acinar lesions on the outskirts, composed of yellow caseous acini surrounding a terminal bronchiole. The older these are the more are they fused together into larger masses, the younger and more distant they are the smaller are they likely to be. They are formed by invasion of the terminal bronchioles by tuberculous granulation tissue so that the corresponding acini collapse and become filled with an exudate which in turn becomes caseous. Just as the acinus is the fundamental unit of lung structure, so the acinar lesions form the fundamental units of the pathology of pulmonary tuberculosis.

So far we have spoken as if the disease were a steadily progressive one, but such is by no means the case. There is fibrosis as well as caseation, and this fibrosis is seen as a thickening of the bronchi, bloodvessels, and pleura,

and as numerous white strands on the cut surface. Chronic cavities have a thick and fairly smooth wall (Fig. 219). Healing of a cavity may occur; this may take place either by scarring or by the cavity becoming filled with caseous material. A cavity of large size, as seen by x-ray, may entirely disappear. Sometimes a cavity may undergo healing in the clinical sense, *i. e.*, it no longer produces sputum filled with tubercle bacilli, and yet remains open, communicating with a bronchus. The caseous lining is shed, the tuberculous granulation tissue becomes fibrosed, and the inner surface of the wall may become epithelialized. A cavity may heal in the pathological sense as the result of occlusion of the draining bronchus, either by obstructive caseous bronchitis, or by the formation of a caseous plug.

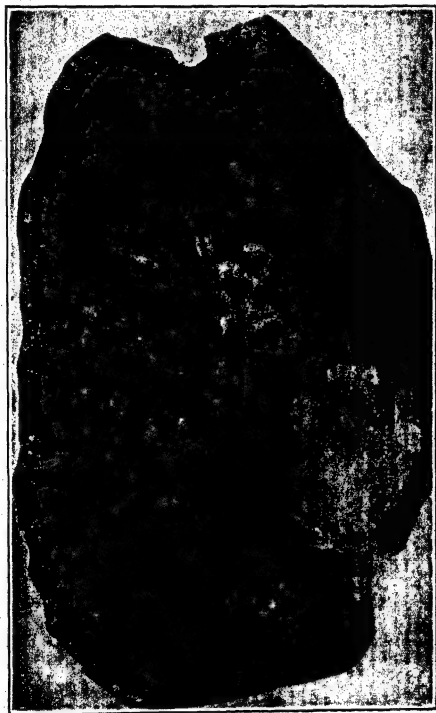


FIG. 220.—Pulmonary tuberculosis showing cavity formation and fibrosis.

When the lungs are freed from the normal pull of the chest by artificial pneumothorax they retract owing to their elasticity, and the cavity shares in this process and tends to collapse and become obliterated. The usual result is a solid nodule due to the retention, inspissation and calcification of the contents of the cavity. Pleural adhesions are very common, especially at the apex, and there may be patches of recent pleurisy. All of this indicates a good defense, and the disease may either remain stationary or may retrogress to a marked degree if the patient receives the best treatment (sanatorium, artificial pneumothorax, etc.). This is the form of tuberculosis which can be treated with such encouraging results, especially in

the early stages. The bronchial lymph nodes are either not involved or only to a slight degree. The five chief characteristics of this type of pulmonary tuberculosis are: (1) consolidation and caseation, (2) cavity formation, (3) acinar lesions, (4) fibrosis, (5) relative escape of the tracheo-bronchial lymph nodes, which contain very few bacilli.

The *microscopic picture* varies in different places. The basic lesion is the tubercle, consisting of epithelioid cells and lymphocytes with the usual addition of caseation and giant cells. As the tubercles fuse to form larger masses caseation becomes marked. Much of the elastic tissue remains intact and holds the caseous material together, but when secondary pyo-

genic infection occurs this tissue is destroyed so that softening soon develops. If the section is stained to show reticulum fibers an abundance will be seen between the cells of the inflammatory exudate, in sharp contrast to what is found in the next form. Proliferation of fibroblasts and fibrosis are very marked, especially in those cases where resistance is good. The arteries may show an endarteritis obliterans which narrows or even closes the lumen, and this prevents hemorrhage if the wall of the vessel should become ulcerated. The surrounding alveoli may contain a cellular exudate, and in the more fibroid forms the alveolar epithelium may become cubical and gland-like (Fig. 211, p. 391).



FIG. 221.—Pulmonary tuberculosis. Consolidation of the entire lung from caseous pneumonia with acute cavity formation in a boy, aged fifteen years.

3. ACUTE TUBERCULOUS CASEOUS PNEUMONIA.—This is an acute form of the disease in which infection overwhelms resistance and sweeps through

the lung, so that it gives rise to the clinical picture of galloping consumption or acute phthisis (wasting). The lesions ulcerate through the walls of the bronchi in many places and the infection is widely spread throughout the lung by inhalation. The lesions no longer remain discrete as they tend to do in the previous form, but fuse together to form large caseous areas which may involve the whole of a lobe or even the entire lung and give a pneumonic appearance like that of gray hepatization, so that the condition is called caseous pneumonia (Fig. 221). Acute cavities may form in the consolidated tissue, but these are seldom very large, and have the ragged lining characteristic of such cavities with none of the fibrous capsule which shuts off a chronic cavity from the surrounding lung. Pleurisy and bron-

chitis are present. The tracheobronchial lymph nodes are enlarged and caseous, for the lung is unable to hold back the bacilli which reach the nodes in great numbers.

The *microscopic picture* is one of rapid caseation and destruction with no evidence of resistance on the part of the tissues. The alveoli are filled with an acute cellular exudate, mainly mononuclear in type, which rapidly becomes caseous so that all detail is lost. Elastic tissue is destroyed, and no reticulum fibers are formed between the cells in the alveoli. Neither giant cells nor fibrosis are in evidence. Smears of the exudate and sections of the lung show enormous numbers of tubercle bacilli, far in excess of what is seen in any other form of pulmonary tuberculosis.

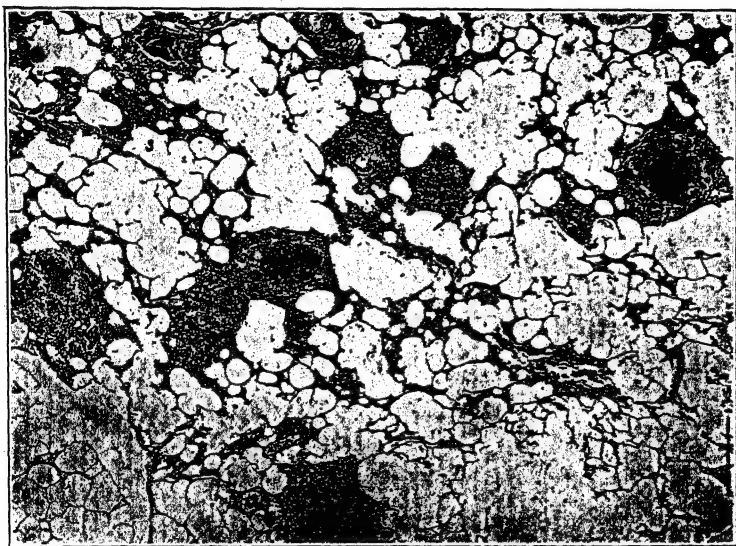


FIG. 222.—Acute miliary tuberculosis of the lung. Between the tubercles the lung tissue is practically normal.  $\times 18$ .

4. ACUTE MILIARY TUBERCULOSIS.—If a caseous tuberculous focus discharges its contents into a bloodvessel the body is flooded with tubercle bacilli. A caseous bronchial lymph node may become adherent to a branch of the pulmonary artery and open into that vessel, in which case only the affected lung may show the tubercles. More often the vessel is a vein, and then tubercles are found in all the organs as well as in the lungs, the patient often dying of tuberculous meningitis.

The lungs are intensely congested and studded with minute tubercles, many of which can only be seen with the aid of a magnifying glass. At first the lesions are pale and translucent, but as caseation develops they become yellow and opaque. *Microscopically* the tubercles are seen to be everywhere in the fibrous framework of the lung, but the intervening alveoli are either empty or contain catarrhal cells (Fig. 222). The tuber-

cles present the usual caseous center, epithelioid cells, lymphocytes, and giant cells.

A distinction must be drawn between tuberculous bacillema and general miliary tuberculosis. A varying degree of bacillema occurs in every case of tuberculosis; it is by this means that discrete foci in bone, kidney, etc., are set up. But it is only when resistance is overwhelmed that the condition becomes miliary tuberculosis, and it is overwhelmed because of the massive size of the dose, especially if this dose be continually repeated. Miliary tuberculosis may occasionally be *chronic* and the lesions may undergo healing by fibrosis.

THE RELATION OF SYMPTOMS TO LESIONS.—The *general symptoms* (fever, loss of weight, asthenia, etc.) are due to the absorption of toxins. They become more marked when secondary infection is added to the pure tuberculous infection. *Cough* is a bronchial symptom due to inflammation of the larger bronchi, the walls of which are much more sensitive than those of the bronchioles. *Pain* in the side is due to a tuberculous pleurisy. The character of the *sputum* depends entirely on the form which the lesions take. In miliary tuberculosis there may be no sputum. As long as the lesion remains closed the sputum remains scanty and contains no tubercle bacilli. When cavities form the sputum becomes abundant and purulent and contains numbers of bacilli. It should be remembered that unless the bacilli number 100,000 per cc. of sputum, they will probably not be seen with the ordinary Ziehl-Neelsen method. Guinea-pig inoculation is a thousand times more sensitive. The appearance of elastic tissue fibers in the sputum indicates lung destruction. *Hemoptysis* marks the end of the beginning or the beginning of the end. In the early stages there may be erosion of a small vessel in the process of softening. In the late stages a large artery crossing a chronic cavity may give way causing a severe and possibly a fatal hemorrhage.

The *physical signs* depend on the character of the lesions. The consolidation and cavitation of the fibrocaseous form are indicated by dullness on percussion, increased tactile fremitus, and blowing breathing which may become amphoric over a large cavity. All these signs are diminished if the pleura is much thickened. There is not the wooden dullness of lobar pneumonia except in the caseous pneumonic form. Moist râles intensified by coughing (post-tussic) indicate breaking down of caseous material; they become coarser as the cavities enlarge. Small calcified lesions, Ghon lesions, miliary tubercles, and, of course, more extensive consolidation and cavity formation are clearly shown by the roentgen rays.

BRONCHOLITHIASIS.—Known also as bronchial calculus and lung stone, this term signifies the presence of calculi in a bronchus. The usual origin is a caseous tuberculous focus in the lung or lymph nodes or the inspissated pus of an old lung abscess. The calculus erodes through the bronchial wall, or it may be formed within the lumen of the bronchus. The calculi, which are often multiple, are hard and irregular. They may be expectorated, or may remain within the bronchial lumen and cause obstruction.

## SYPHILIS OF THE LUNG

Syphilis of the lung may be congenital or acquired. The former is much commoner and much more characteristic than the latter.

The *congenital form* is seen in syphilitic infants. The child is either born dead or dies in a few days. The lung or part of it is consolidated so that it sinks in water, and is of a pale gray color. For this reason the condition is called *pneumonia alba*. It is an interstitial pneumonia caused by enormous number of spirochetes scattered through the lung, with the formation of a large amount of cellular fibrous

tissue (Fig. 223). The alveoli are small, separated by the fibrous tissue, and lined by cubical epithelium so as to have a gland-like appearance. The picture is one of arrested development rather than active inflammation. I have seen nodular lesions, like gummata in the gross.

The *acquired* form is now so rare that it need only be mentioned. The usual lesion is ulceration of a bronchus with subsequent scarring and bronchial obstruction. Gummata are a remote possibility.

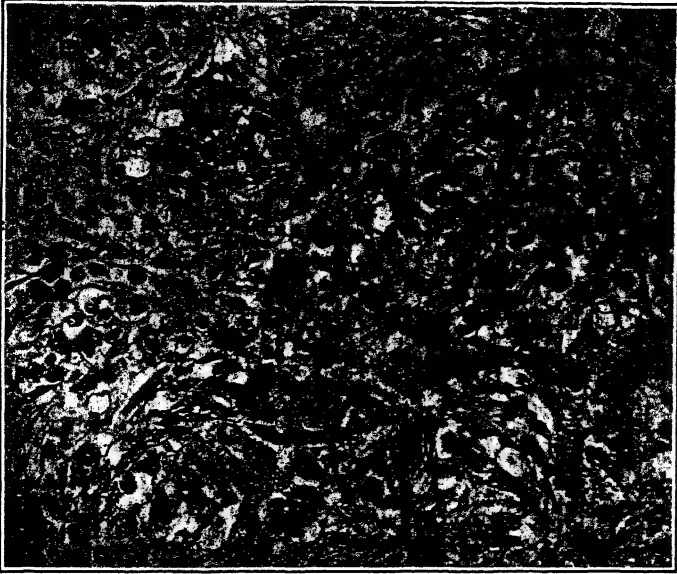


Fig. 223.—Congenital syphilis of the lung.  $\times 300$ .

## MYCOTIC INFECTIONS OF THE LUNG

Mycotic diseases of the lung due to the higher fungi are easily confused with tuberculosis even in the autopsy room, for caseation and cavity formation are among the chief features. The only certain method of distinction is the finding of the organisms in the tissue.

**BLASTOMYCOSIS.**—This is probably the commonest of the pulmonary mycoses. The spores may be inhaled directly, or infection may spread by the blood stream from skin lesions to the lung. The lesions (consolidation and cavitation) are very much like those of tuberculosis, but there is more suppuration and giant-cell formation. The blastomycetes are seen in the microscopic sections in large numbers and also in the sputum and pus. The prognosis is far worse than in tuberculosis.

**ACTINOMYCOSIS.**—The actinomyces are inhaled into the lung or spread from the mouth. They never spread by the blood stream. The lesions are like those of fibrocaceous tuberculosis, but instead of cavitation there is abscess formation. Moreover the lower lobe is most often involved. As usual the disease spreads by contiguity, not by the lymph or blood stream, so that it extends to the chest wall, spine, and through the diaphragm, forming numerous sinuses, but not involving the bronchial lymph nodes or distant organs. The fungus is found in the "sulphur granules" in the pus and sputum. The disease is usually fatal in from six months to a year.

**STREPTOTHRICOSIS.**—A rare infection by a branching fungus. The pulmonary lesions are of the septic type—abscess, gangrene and bronchiectasis. The infection may spread by the blood stream to the brain and elsewhere.

**ASPERGILLOSIS.**—This is caused by *Aspergillus fumigatus*, a filamentous fungus with a basal stem and a stalk supporting a spore-bearing head. The disease occurs amongst bird fanciers, pigeon stuffers, and other grain handlers. The lesions are similar to those of tuberculosis, with necrosis and cavitation. Mats of mycelial threads may be seen in some areas. The x-ray picture may strongly suggest miliary tuberculosis or silicosis.

**MONILLIASIS.**—The fungus, *Monilia*, may cause pulmonary lesions which resemble those of tuberculosis. Small yellow nodules fuse together, break down and give rise to cavities. The microscopic picture is similar to that of tuberculosis, but the necrotic center contains monilia threads. One must not, however, make the mistake of thinking that monilia in the sputum proves that the patient is suffering from pulmonary monilliasis.

**COCCIDIOMYCOSIS.**—The characteristics of the fungus *coccidioides* are described in Chapter 7. The infection is widespread throughout Southern California, West Texas, and the regions of the United States bordering on Mexico. The spores of the fungus are inhaled from the soil, causing an acute pneumonia. While this usually clears up completely, many cases have incomplete resolution with residual infiltrations, of which nodular densities and cavities are the most characteristic x-ray feature. These may persist for many years unchanged. The residual pulmonary lesions, especially the cavities, may strongly suggest tuberculosis, but the patient presents no symptoms and feels quite well. Infection does not spread to other parts of the lung nor to distant organs. The fatal disseminated form of coccidioidal infection is a very different story.

**HISTOPLASMOSIS.**—Like coccidiomycosis, histoplasmosis used to be regarded as a fatal systemic fungous disease. It is now known that a mild form exists. The geographic distribution is marked, namely the Mississippi valley and the Eastern Central states of North America. There is an unusually high incidence of pulmonary calcification with a negative tuberculin but a positive histoplasmin reaction in these areas, and there can be no doubt that this calcification indicates healed lesions in a benign form of pulmonary histoplasmosis. Nodular foci and cavities have been found in the lungs.

## CIRCULATION DISTURBANCES OF THE LUNG

**Active Congestion.**—This is rather an ill-defined condition which may be the result of irritating gases or the initial stage of an acute inflammation. The vessels in the alveolar walls are distended with blood.

**Passive Congestion.**—In passive congestion the dilatation of the vessels is a passive affair due to mechanical causes. Two forms are recognized: (1) brown induration, a chronic process, (2) hypostatic congestion, usually a terminal one.

**Brown Induration.**—This is due to some central obstruction to the circulation, and is best seen in mitral stenosis, the blood accumulating in the lung. The lungs are voluminous, russet-brown in color, tough, and indurated (brown induration). *Microscopically* the lung is filled with blood, the alveolar vessels being widely distended, and the alveoli containing many red blood cells. The characteristic feature is the presence of great numbers of large phagocytic cells filled with yellow pigment. These cells are known as *heart failure cells* even when they occur in other than cardiac



conditions, and may be derived from residual epithelial cells in the alveolar walls known as septal cells or epicytes (Macklin) or from histiocytes (reticulo-endothelial cells) (Fig. 224). The pigment is hemosiderin, derived from the red blood cells in the alveoli, and gives the Prussian blue reaction for iron. There is also a marked increase in the connective tissue of the lung, which is partly responsible for the toughness and induration. This is probably caused by the pigment, which is carried by phagocytes into the lymphatics and distributed throughout the framework of the lung, where it excites fibrosis. The alveolar walls are thickened, so that the vascular endothelium is separated from the air in the alveoli. This interferes with oxygenation of the blood, and is responsible for some of the dyspnea of mitral stenosis. Hemoptysis is a common symptom of



FIG. 224.—Heart failure cells in the lung. The alveolar walls are greatly thickened.  
× 250.

mitral stenosis, and is due to the hemorrhage into the alveoli. The blood in the alveoli is partly converted into bilirubin, and the bilirubin content of the plasma may be above normal, so that mitral stenosis is one of the conditions which may give rise to a latent jaundice.

**IDIOPATHIC PULMONARY HEMOSIDEROSIS.**—This rare condition, also known as essential brown induration of the lungs, is a disease of children. The lungs show an extreme degree of brown induration, but no cardiac or other lesions can be found to account for this. There are periodic attacks of severe anoxic anoxemia associated with massive intra-alveolar diapedesis of red cells. At autopsy the alveolar walls are thickened, the capillaries greatly dilated, and the alveolar spaces filled with red cells and macrophages containing hemosiderin. The cause is unknown.

**Hypostatic Congestion.**—An accumulation of blood in the lower and posterior part of the lung is found at every autopsy, and is due to relaxation of the vessels

after death plus the force of gravity. A much more advanced condition is found in patients with some debilitating illness and weak heart action who have been kept on their back. The dependent part of the lung may appear to be consolidated, so that without the microscope it may be impossible to tell if the condition is hypostatic congestion or hypostatic pneumonia. The air in the alveoli is replaced by plasma and red blood cells, but a pneumonic process may be added as the result of terminal infection.

**Edema.**—A slight degree of pulmonary edema is almost as common as congestion and may be seen at the base of the lung in nearly every autopsy. It is due to failure of the heart as the patient is dying. Pronounced edema may take two main forms, inflammatory and mechanical.

**INFLAMMATORY EDEMA.**—This forms a part of any inflammatory exudate, the plasma readily passing from the vessels into the lumen of the alveoli. The amount varies depending on the irritant. It is very abundant in influenzal pneumonia, where the lung becomes water-logged. A varying amount of the plasma is converted into fibrin, the proportion being extremely large in pneumococcal pneumonia. The increased capillary permeability characteristic of shock results in edema. Many cases of so-called terminal edema are of this nature.

**MECHANICAL EDEMA.**—This variety is due to chronic heart failure. The edema is due, as Welch showed in experimental work on animals, to a disproportion between the working power of the two ventricles. If the left ventricle fails more rapidly than the right, the pulmonary vessels become distended and plasma leaks through the capillary walls into the alveoli. If we ask *why* the fluid leaks through, we find ourselves confronted with the difficult problem of edema which has already been discussed in Chapter 3.

Pulmonary edema of the mechanical type is naturally a chronic condition. An *acute pulmonary edema* may occasionally develop, for which no adequate cause can be found at autopsy. The patient usually has chronic nephritis or high blood-pressure, and it appears as if some sudden strain had been thrown on the left side of the heart. An acute and fatal pulmonary edema may follow a surgical operation; I have seen this accident occur in a simple appendectomy. In rare cases acute edema of the lung may come on after removal of a pleural effusion. Here the lung which has been compressed for a long time suddenly expands, and for some reason fluid pours from the vessels into the alveoli.

The *gross appearance* of the lung is characteristic. It is voluminous, heavy, firm, or doughy, and shows marked pitting on pressure. In the mechanical variety the edema is most marked in the dependent parts of the lung (base and posterior border). The consolidation may be so marked as to simulate pneumonia, but steady pressure will force the fluid out and leave the lung soft. When the lung is cut and squeezed, water pours from the cut surface and from the bronchi. If the condition is very marked as in influenzal pneumonia or acute edema of the lung the fluid pours out of the water-logged organ without any pressure being used. The color of the fluid depends on the presence or absence of congestion. If this is marked the fluid is bloody, if absent the fluid is clear and watery.

The *microscopic picture* is that of alveoli filled with fluid coagulated by the fixative (Fig. 225). The more albuminous the fluid, the more intensely

dose it stain with eosin. If the fluid has a very low protein content (mechanical edema), it may tend to be washed out by the fixative. In such cases the edema is best demonstrated by fixing the tissue for a few moments in boiling formalin which coagulates the fluid *in situ*. The material which fills the alveoli appears as a hyaline sheet, but sometimes it is granular. In inflammatory edema there may be a varying amount of fibrin formation.

**Embolism and Infarction.**—This subject is fully discussed in connection with the general question of embolism in Chapter 3. The thrombosis which precedes the embolism is often postoperative, especially after operations on the female pelvis, but the condition is even more frequent in purely medical (chiefly cardiac) cases. The first embolus may prove fatal. As a rule, however, a fatal embolus is preceded by a number of smaller emboli which can be detected clinically and recognized as danger signals. In this case the use of anti-coagulants such as heparin and dicumarol can arrest the formation of thrombi in the veins and thus protect the patient against fatal embolism. In practice this procedure has proved of value. Ligation of the veins in the leg has a similar effect. If the embolus is large and blocks a main artery death may occur in the course of a few minutes from shock. In this case there is no time for an infarct to be produced. Death is apparently due to widespread vasoconstriction, as section of the sympathetic nerves in animals prevents it. When the embolus is smaller a red infarct is formed with hemorrhage into the alveoli, hemoptysis, and pain in the side due to a patch of pleurisy over the infarct. When the infarct is larger there may be a hemorrhagic pleural effusion.

As recovery takes place the infarct is partly absorbed, partly replaced by a scar which can seldom be detected if the patient dies later. If, however, formalin is instilled into the trachea and the lungs are then inflated to their original size, healed infarcts can often be demonstrated. Chronic pleuritis and puckering are easily mistaken for healed tuberculosis. Persistence of elastic tissue and the demonstration of an organized embolus help to distinguish a healed infarct from tuberculosis. Further details will be found in Chapter 3.

**FAT EMBOLISM.**—As a result of fracture, crushing injuries, and traumatic lesions of fat, globules of fat may enter the torn veins and be carried to the lungs. Here they seldom do much damage, but if present in very large amount there may be dyspnea and prostration. The gross appearance of the lung is normal, but in frozen sections stained for fat, globules and cylinders are seen in the capillaries.

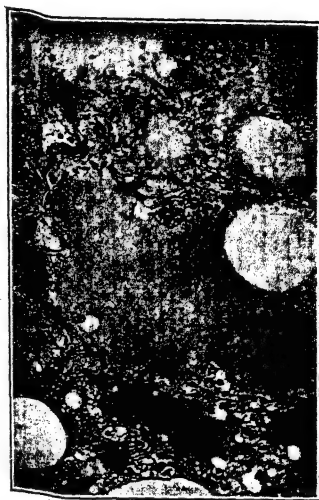


FIG. 225.—Edema of the lung. The acini are filled with albuminous fluid.  $\times 150$ .

If the fat passes through the lung it may reach the kidneys and be excreted, or it may lodge in the brain with fatal results.

### ATELECTASIS

Atelectasis literally means incomplete expansion (*ateles*, incomplete + *ektasis*, expansion), but it is now synonymous with collapse of the lung. This may be: (1) compression, (2) obstruction, or (3) congenital.

**ACUTE MASSIVE COLLAPSE.**—This peculiar and rare complication is a special example of obstructive atelectasis caused by the two factors, bronchial obstruction and respiratory weakness. The clinical picture is a striking one. From a few hours to a few days after an operation, usually abdominal, the patient suddenly develops the symptoms of an acute thoracic catastrophe, *i.e.*, extreme dyspnea, marked cyanosis, and collapse. There is no respiratory movement on the affected side, the heart is displaced to that side, there are physical signs of consolidation of the lung, and the roentgen-rays show a peculiarly dense shadow and the dome of the diaphragm high and immobile on the side of the collapse. There is at present no really satisfactory explanation of the condition.

**CONGENITAL ATELECTASIS.**—This is the only form of collapse which deserves to be called atelectasis, for the alveoli have failed to expand. It is seen in the stillborn child who has never breathed, and in children who live only a few days and never breathe well, the lung shows many areas of atelectasis. The lung is dark, firm, and airless. If only a part is collapsed, that area is depressed below the surrounding surface. The collapsed lung sinks in water, a convenient practical test to determine if the child has breathed. The lung may have to be cut into separate pieces, for a small part may have become expanded. It is commonly stated that the alveolar epithelium of the full term fetus is cuboidal in form, giving the alveoli a gland-like appearance. This is not correct. It is true for the earlier stages of development, but after the fifth month the cuboidal epithelium begins to disappear and the alveoli to be opened up. The difference between the lung which has inhaled air and the one which has not is quantitative rather than qualitative. As the result of extra-uterine respiration the alveoli are more fully distended and their walls are thinner than if the child has never breathed. If the body has been kept for some time in a warm room the lung may float due to the production of gas by putrefying bacteria. In such cases bubble-like areas are seen microscopically in the septa and alveoli; these are easily distinguished from alveoli partially distended as the result of intra-uterine respiration.

**Compression Atelectasis.**—Pressure on the lung drives out the air and produces collapse. This may be *complete* when the pressure is great and uniform as in massive pleural effusion, empyema and pneumothorax, but only *partial* when the pressure is more local as in pressure by a tumor, an enlarged heart, or an elevated diaphragm. When the pressure is removed the lung will expand again, but lesions may be formed (as in empyema) which may prevent re-expansion.

**Obstructive Atelectasis.**—In this form two factors are nearly always at work, obstruction of a bronchus and weakening of the respiratory movements (chest or diaphragm). If obstruction is due to a foreign body in a bronchus the second factor will not be present, but usually it is caused by an accumulation of mucus in the bronchioles associated with poor respiratory movements. If deep breathing and coughing were possible the ob-

struction in the bronchioles would be cleared away. This type of atelectasis is commonest in debilitated children suffering from bronchitis, bronchopneumonia, etc. Indeed in such children even the normal amount of mucus in the bronchioles may lead to partial collapse. The two factors are present after an abdominal operation, for the anesthetic will stimulate the bronchial secretion, and the abdominal section will prevent the patient from breathing deeply. In all of these instances the air in the affected part of the lung is absorbed into the blood, no more air can enter on account of the obstruction, and that part of the lung collapses.

**MORBID ANATOMY.**—The condition of the lung is similar in all forms of atelectasis, whether congenital, acquired, or massive. In the massive form and in compression due to pleural effusion or pneumothorax the entire lung may be so collapsed that it no longer fills the cavity but lies against the posterior chest wall and vertebral column like a squeezed sponge. If only some parts are affected, these are firm, inelastic, airless, and sunk below the surrounding surface. These areas are steel-blue or slate-gray due to stasis of the circulation.

*Microscopically* the alveolar walls are pressed together so that the lumen is nearly obliterated (Fig. 226). In the congenital form the fetal structure is still evident. If the collapse is of long duration fibrosis may occur which will prevent full expansion.

## EMPHYSEMA

Emphysema is the opposite of atelectasis. The word means inflation, and the alveoli are distended instead of collapsed and their walls are atrophic. Emphysema is usually general and affects both lungs. It is a complication of diseases in which there is much coughing or violent expiratory efforts. It usually comes on slowly as the result of chronic bronchitis, pulmonary tuberculosis, etc. Sometimes it is more acute in onset following whooping cough or bronchial asthma. It is said that the playing of wind instruments is a causal factor, but this is probably a myth. If the patient plays in a band he is as likely to perform on the big drum as on the trombone. The local form is probably compensatory in nature, being found in the neighborhood of areas of consolidation and collapse. It seems fair to say that the essential cause of emphysema is still unknown.

**MORBID ANATOMY.**—The lungs are very voluminous, very pale, and quite dry. The heart may be completely covered, so that there is no

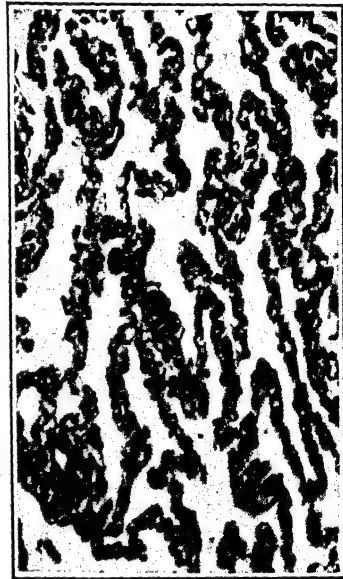


FIG. 226.—Atelectasis.  $\times 225$ .

cardiac dullness on percussion. Large blebs or bullæ project on the surface in the more poorly supported regions (apex, anterior margin, base). The lung has a peculiarly soft, dry, feathery feel. There is marked pitting on pressure due, not to edema, but to destruction of the elastic tissue. *Microscopically* the lung presents a delicate lace-like structure. The air vesicles are few in number and of great size. This is not due to breaking down of septa between the alveoli. Normally the alveoli present for the most part a closed appearance, because the lung is collapsed and random sections do not pass through the alveolar mouths as often as in expanded lungs. When the normal lung is fixed in a distended condition the alveoli open into the alveolar ducts, so that the walls may appear to be ruptured. The three

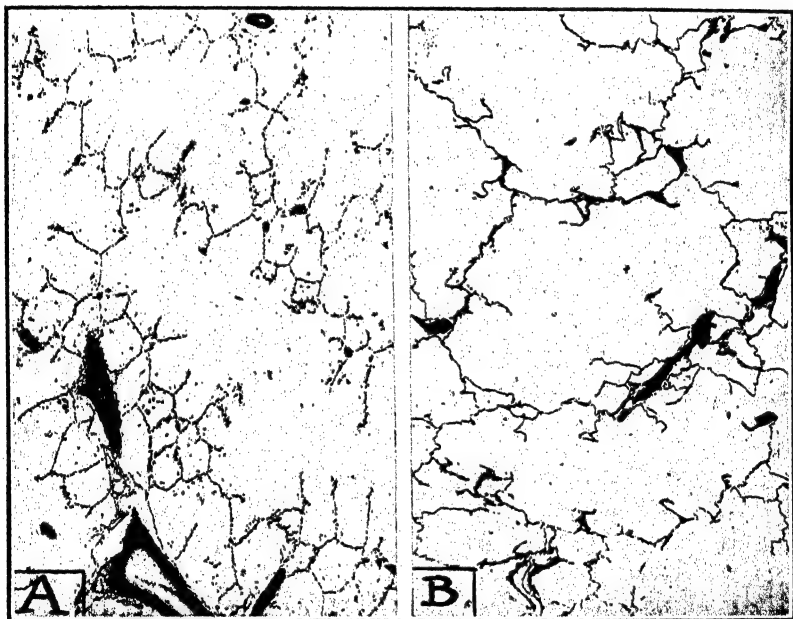


FIG. 227.—Emphysema. A, Normal lung.  $\times 36$ . B, Emphysematous lung, showing increase in alveolar diameter, flattening of alveolar bases and loss of zig-zag lines.  $\times 36$ . (Boyd, Pathology of Internal Diseases.)

criteria which Hartroft suggests as pathognomonic of the emphysematous lung are: (1) marked decrease in the average alveolar depth, (2) a corresponding increase in the average alveolar diameter, and (3) flattening of the alveolar bases with loss of the zig-zag lines which form so striking a feature of the normal lung fixed in an expanded condition (Fig. 227). As a result of these changes there is a great diminution in the volume of the capillary bed. It is this avascularity which is responsible for the pallor of the lung, for the dryness of the cut surface, and for the obstruction to the pulmonary circulation.

In emphysema, and to a lesser extent in other chronic diseases of the lung, the broncho-pulmonary veins which drain the bronchi, bronchioles and

pulmonary interstitial tissue are greatly enlarged (Liebow). These veins, which were first demonstrated by Zuckerkandl by means of injection in 1882, communicate both with the pulmonary and the azygos veins. They, therefore, act as a bypass when the pulmonary veins are occluded, and constitute a shunt between the right and left auricles. The flow at first is from left to right, but in advanced emphysema the valves between the broncho-pulmonary-azygos junctions become incompetent, and the flow may then be reversed. The expansion of the broncho-pulmonary venous circulation may be compared with the expansion of the arterial collateral circulation which has been demonstrated so beautifully by Liebow in bronchiectasis, but the two do not necessarily go hand in hand.

**EFFECTS.**—The effects of emphysema are far-reaching and serious. The chest has a barrel-shaped appearance, the ribs being raised and the sternum pushed forward, so that the antero-posterior equals the transverse diameter. The costal cartilages are calcified so that the thorax is fixed in an expanded condition. The lungs are hyper-resonant, and the area of superficial cardiac dulness obliterated. Respiratory movements are diminished, and expiration is difficult and prolonged. Owing to the vascular occlusion there is marked obstruction in the pulmonary circulation, so that there is great hypertrophy and dilatation of the right ventricle and general venous congestion throughout the body. The pulmonary artery may show arteriosclerosis, just as it does in the obstruction due to mitral stenosis. Dyspnea and cyanosis develop, with a compensatory increase in the number and size of the red blood corpuscles. One of the emphysematous bullæ may rupture into the pleural cavity, giving rise to spontaneous pneumothorax.

**ATROPHIC EMPHYSEMA.**—This condition is seen in old age (senile emphysema) and in wasting diseases. It is not a true emphysema, for there is no distention of the alveoli, no enlargement of the lungs, no bullæ on the surface. The only resemblance lies in the microscopic picture, where there is atrophy and disappearance of the walls of the alveoli so that large spaces are formed. The condition is an atrophy from defective nutrition, and does not deserve to be called emphysema.

**INTERSTITIAL EMPHYSEMA.**—This also is not a true emphysema. The air escapes from the alveoli and makes its way into the interstitial tissue of the lung, particularly along the perivascular sheaths, as a result of which there may be serious pressure on the vessels. This is usually due to tearing of the lung by a fractured rib, wound, etc., but in children it is sometimes caused by overdistention and rupture of the alveoli during the violent paroxysms of whooping cough. The air collects in the lymphatics in the form of tiny beads, which are best seen under the pleura. It may then pass to the mediastinum and from there to the neck and down over the chest wall. The lung and the subcutaneous tissues have a peculiar and quite characteristic crackling feel.

## TUMORS OF THE LUNG

**Carcinoma.**—Primary cancer of the lung or bronchogenic carcinoma used to be regarded as a rarity, but during the past quarter of a century it has become one of the commonest, if not the commonest, of the killing cancers, especially in men. Indeed it has been said that it is important to think of a pulmonary neoplasm when a patient in the cancer age, showing no symptoms of cardiac, renal or arterial disease, begins to cough and is short winded.

There has been much discussion as to whether this increase is real or only apparent, and if real, what has caused it. The answer is that we do not know, because there are no figures on which the death rate from intra-thoracic cancer of half a century ago can be compared with that of today. One can read papers proving that the increase in one country, such as Great Britain, is real (Kennaway and Kennaway) or that it is only apparent (Passey and Holmes). It was not until the beginning of the present century that coronary thrombosis and myocardial infarction were recognized, but no one suggests that the disease started then. There can be no doubt that the disease is recognized much more frequently nowadays by the internist, the radiologist, the bronchoscopist, the pathologist and the thoracic surgeon. Goethe once remarked "Was man weiss, sieht man," and we recognize what we know to be common. It is also possible that there may be a true increase, due to the action of some new carcinogen. Ochsner points out that from 1938 to 1948 the fatal cases of bronchogenic carcinoma increased 144 per cent, whilst the total cancer deaths increased only 31 per cent. In 1920 this tumor constituted only 1 per cent of cancers: in 1948 the figure was 8.3 per cent. He hastens to add that this striking increase parallels the increase in cigarette smoking. There has been a tremendous increase in the incidence in Britain in the last 25 years, as much as 15 fold according to Doll and Hill. The corresponding figure in the United States for a similar period is about half that amount. The mortality from cancer of the stomach has been stationary. On the other hand Steiner, in an analysis of the material examined in the Department of Pathology of the University of Chicago during the forty-year period between 1902 and 1941 came to the conclusion that there was no real increase in the frequency of bronchogenic carcinoma.

In respect to the development of lung tumors, the genesis of pulmonary tissue becomes of importance. There has long been controversy as to the ultimate structure of the pulmonary alveolus. As the result of observations on the fetus in *utero* and in transplants in the anterior chamber of the eye Waddell came to the conclusion that the cells which line the bronchi and alveoli originate from mesoderm. This revolt against the time-honored theory of the specificity of germ layers is not really new; after all, such epithelial structures as the liver and kidney are of mesodermal origin. The mesodermal origin of bronchial epithelium would serve to explain the marked pleomorphism and the occurrence of sarcomatous elements in bronchial cancer, the sarcomatous changes in transplanted pulmonary carcinomas, and the frequent occurrence of neoplastic cartilaginous and osseous tissue in bronchial adenomas.

**ETIOLOGY.**—The literature is full of etiological theories, most of which are purely fantastic and will not be mentioned. One definite fact must have significance, but unfortunately its meaning is obscure; the sex incidence is extremely marked, from 80 to 90 per cent occurring in the male. This may point to a hormonal influence or to an occupational hazard. The most striking examples of occupational cancer of the lung are the cobalt miners of Schneeberg and the pitch-blend and uranium miners of neighboring Joachimsthal, both in Czechoslovakia. In both cases the air of the mines is highly radio-active. For 450 years the underground miners of Schneeberg have been dying of a chest complaint now known to be cancer of the lung, whilst in Joachimsthal 90 per cent of all malignant tumors occur in the lung. Other occupations which carry the hazard of bronchial cancer are workers in chromate plants (although chromium compounds are not known to be carcino-



genic), stokers inhaling hot tar fumes in generator plants, and asbestos workers. There is no significant relationship between silicosis (nor tuberculosis) and cancer of the lung. Other carcinogens may be inhaled more by men than women, but no certain facts are known.

Cigarette smoking has been incriminated. There is no experimental evidence that tobacco smoke has a carcinogenic action on bronchial epithelium, but the clinical evidence is suggestive even though statistics are notoriously misleading. Wynder and Graham found that of 605 patients with cancer of the lung 51 per cent smoked more than twenty cigarettes a day, whilst only 1.3 per cent were nonsmokers; in the general hospital population the corresponding figures were 14.6 per cent and 19.1 per cent. The sale of cigarettes in the U. S. A. has paralleled the increase of lung cancer. One of the few places where the disease is known to be rare is Iceland.



FIG. 228.—Carcinoma cells in sputum.  $\times 630$ .



FIG. 229.—Origin of bronchogenic carcinoma from bronchial epithelium.  $\times 75$ .

This may be associated with the fact that cigarette smoking has increased much more slowly in that country than in lands where lung cancer is common (Dungal). An outstanding critical contribution from the statistical side is that of Doll and Hill who investigated the smoking habits of patients with cancer of the lung, stomach and large bowel from twenty London hospitals, as well as a control group who did not have cancer. They came to the conclusion that smoking is an important factor in the causation of carcinoma of the lung, and suggest that above the age of forty-five the risk of developing the disease may be fifty times as great among those who smoke 25 or more cigarettes a day for many years as among non-smokers.

**SYMPTOMS.**—The chief symptoms are cough, blood-stained sputum, dyspnea, and pain in the chest. These symptoms are due partly to pressure, partly to bronchial obstruction. There may be pressure on any of the structures in the chest. Pleural effusion occurs in about 50 per cent of the cases and is often blood-stained. Fever and leucocytosis are occasional symptoms which tend to confuse the diag-

nosis. The diaphragm on the affected side is drawn up to a remarkable degree (tenting of the diaphragm) as seen in the roentgen-ray film. The film often fails to indicate any tumor, merely showing such effects of the tumor as atelectasis, pleural effusion, enlarged mediastinal glands, etc. In secondary carcinoma, on the other hand, the tumor itself can be readily seen. Although the patient is usually in the cancer age, I have seen a number of cases under twenty-five years of age. Bronchoscopic examination is of great value; it may show a definite tumor, mucosal roughening, stenosis, or merely interference with the normal movements. It is usually possible to obtain a fragment of tumor for biopsy through the bronchoscope. The breath sounds are remarkably absent over the affected area, even though the bronchi may not be correspondingly narrowed on bronchoscopic examination.

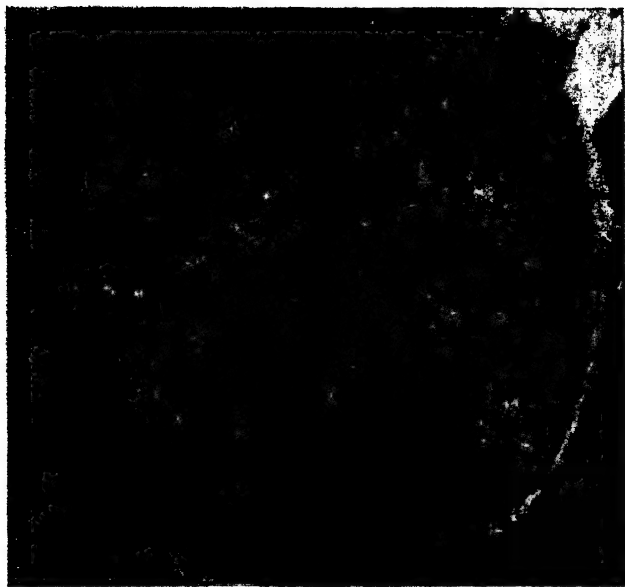


FIG. 230.—Primary carcinoma of the lung. Part of the new growth is the lung tumor, but part is the greatly enlarged bronchial lymph nodes.

Cancer cells exfoliated from the tumor can often be found in the sputum or in fluid obtained by bronchoscopic aspiration (Fig. 228). The material can be smeared, or, preferably, coagulated and treated as a tissue. The more frequent the examination, the more likely are cancer cells to be found. The procedure is of marked diagnostic value. A negative finding is of no significance.

**LESIONS.**—Carcinoma of the lung is essentially bronchogenic in origin (Fig. 229). The gross appearance varies to an extraordinary degree, which is one of the reasons why in the past the correct diagnosis has been so often missed in the autopsy room. The most common finding is a firm grayish-white tumor arising from a bronchus to a lobe rather than from a main stem bronchus. It may project into the lumen as a papillary mass which may block the bronchus and cause atelectasis. (Plate X.) The nature of such a lesion is self-evident. But it may merely cause a white fibrous thickening of the bronchial wall with narrowing of the lumen and only a

## PLATE X



### Bronchogenic Carcinoma

The carcinoma is arising from and occluding a bronchus to the lower lobe. The corresponding part of the lung and the pleura are infiltrated with tumor.

suggestion of roughening of the mucosa. If one is not familiar with the existence of this type of lesion the diagnosis will probably be missed. Not rarely a microscopic examination of the suspected lesion is necessary before a definite report can be given. The size of the tumor varies greatly. It may be no more than 1 to 2 cm. in diameter and yet may have caused large and multiple metastases responsible for the death of the patient. Usually, however, it extends outward for a considerable distance into the surrounding lung, and may fuse with the enlarged bronchial lymph nodes (Fig. 230). In a relatively small number of cases the tumor arises in the peripheral part of the lung from a small bronchus; such tumors tend to be more circumscribed, and are those best suited for surgical removal. The rest of the lung may show a few or many smaller nodules, representing spread along the lymphatics.

Secondary changes may greatly alter the gross appearance. These changes are atelectasis, bronchiectasis and abscess formation. If a main bronchus is blocked a lobe or the entire lung may be completely collapsed. Massive pleural effusion often blood-stained may add to the collapse. A lobe or a lung may be riddled with bronchiectatic cavities, which may develop into abscesses. Sometimes the tumor itself is so completely destroyed by the abscess that microscopic examination is necessary to detect its presence.

The *microscopic appearance* is most varied. There is perhaps no tumor which is so pleomorphic as cancer of the lung, and this explains why in the past it has been so frequently mistaken for other tumors. The cells vary from the most undifferentiated or anaplastic to the most fully differentiated. Three main types can be distinguished, the epidermoid, the anaplastic and the adenocarcinomatous. As the anaplastic may be regarded as an undifferentiated variety of the epidermoid, it may be better to speak of two forms, epidermoid and adenocarcinoma. There is a striking sex difference between the two. Thus in Evarts Graham's experience 94 per cent of the male cases were epidermoid or anaplastic, whilst 35 per cent of the females were adenocarcinoma. The relationship to excessive and prolonged cigarette smoking is well marked in the epidermoid group, but is non-existent in the adenocarcinomas. This suggests the possibility that the two are different diseases due to different carcinogens. In the epidermoid type differentiation is seldom marked, so that the line between this and the anaplastic type may be indefinite, but sometimes fully formed epithelial pearls are present (Fig. 231). The development of the tumor may be preceded by metaplasia of the cylindrical bronchial epithelium into a squamous form, but this is not necessary nor indeed usual. In the anaplastic variety (Fig. 232) the cells are spheroidal or oval (oat-cell type) or even spindle-shaped. These are the tumors which used to be regarded as mediastinal sarcoma, a very frequent diagnosis at the beginning of the century, when bronchogenic carcinoma was regarded as a rarity. The adenocarcinoma is much the rarest. The cells, which may produce an abundance of mucin, are arranged around gland spaces (Fig. 233), into which papillary processes may project. The stroma varies greatly in amount and density. Epidermoid carcinoma arises more insidiously, is of slower growth, and spreads electively to the lymph nodes, whereas the

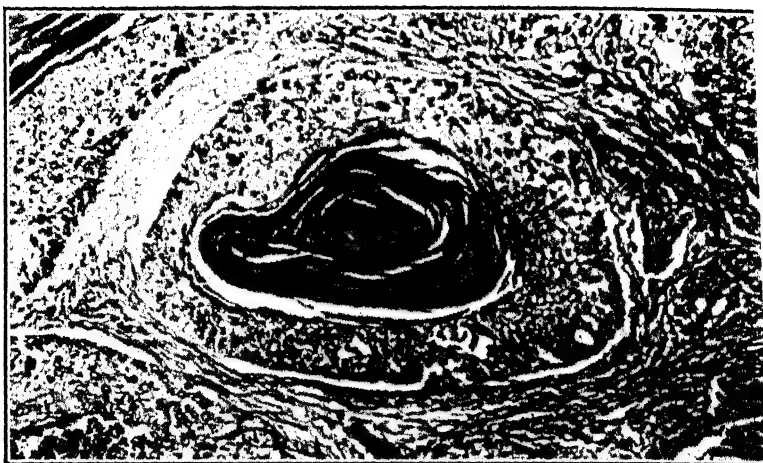


FIG. 231.—Epidermoid.  $\times 150$ .

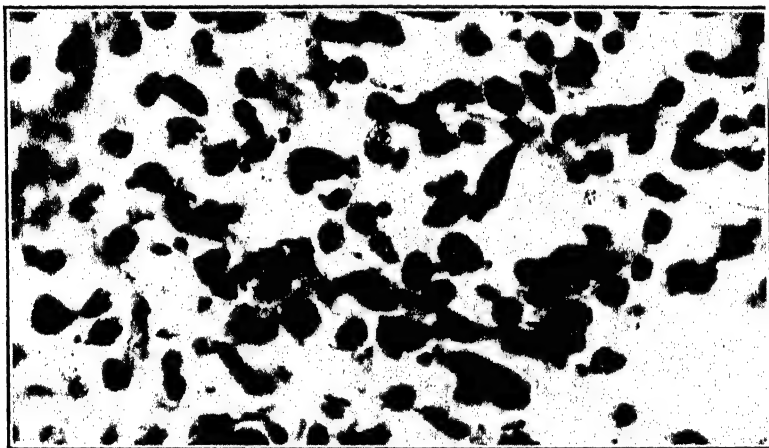


FIG. 232.—Anaplastic.  $\times 700$ .



FIG. 233.—Adenocarcinoma.  $\times 325$ .

FIGS. 231, 232, 233.—Bronchial Carcinoma.

anaplastic form, being undifferentiated, behaves in more explosive fashion, invades the vessels and spreads by the blood stream. These statements of course are merely generalizations to which there are many exceptions.

**SPREAD.**—The tumor tends to spread far and wide and the secondary growths may be the first announcement that there is anything wrong with the patient. Spread is threefold: (1) through the lung, (2) to the lymph nodes, and (3) to distant organs. *Spread through the lung* is mainly by way of the perivascular and peribronchial lymphatics with the formation of new nodules at a distance from the primary tumor (Fig. 234). The tumor cells may also creep along the bronchioles and form a new lining for the alveoli. There may be extension to neighboring structures (pericardium, heart, etc.).



FIG. 234.—Dilated perivascular lymphatics filled with tumor cells. The lumen of the vessel contains red cells.  $\times 175$ .

*Spread to the lymph nodes* is constant; first the regional nodes (tracheobronchial and mediastinal), but later more distant glands (supraclavicular, cervical, and retroperitoneal) may be involved. The mediastinal mass may be larger than that in the lung, and in the past a diagnosis has often been made of mediastinal sarcoma with secondary growth in the lung.

*Spread to distant organs* is very common. The order of frequency is as follows: (1) liver, (2) brain and bone, (3) kidney and adrenal (Fig. 235). Less commonly the pancreas, thyroid, etc., may be involved. The combination of metastases in brain and adrenal is remarkably common. In my material half the cases of all secondary tumors of the adrenal were due to bronchogenic carcinoma. The route of spread from lung to adrenals is probably mainly lymphatic *via* the abdominal lymph nodes, which receive

efficients from both adrenals. The adrenals have direct lymphatic connection with the diaphragm and posterior mediastinum. In one case direct extension could be traced from a tumor in the hilum down through the mediastinum to the left adrenal. Tanner and Gordon believe that the anaplastic form invades the adventitia of the aorta and spreads by the celiac axis and other branches to the adrenals and pancreas. The brain metastasis is often mistaken clinically for a primary cerebral tumor, because the cerebral symptoms may precede the pulmonary ones.

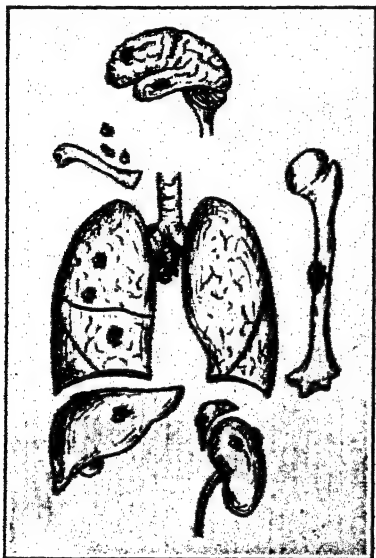


FIG. 235.—Diagram to illustrate sites of metastases in bronchogenic carcinoma.



FIG. 236.—Adenoma of bronchus.  
× 275.

**THE RELATION OF SYMPTOMS TO LESIONS.**—The symptoms are due to pressure and obstruction. The persistent *cough* is due to irritation of a bronchus by the growth. *Bloody sputum* or actual hemorrhage is caused by ulceration of the bronchial mucosa. Occlusion of the bronchus leads to *atelectasis* with displacement of the heart and limitation of movement on the affected side. *Dyspnea* is a common and marked symptom and is probably due to *partial* blocking of a main bronchus, thus interfering with the ventilation (aeration) of a lobe or an entire lung. If the obstruction is complete and the other bronchi are patent there is no dyspnea because the lobe or lung is completely collapsed, there is no partial circulation through it, so that the aerated blood is not polluted by impure blood from the obstructed portions. This is also true of *cyanosis*, although not to the same extent. *Pain* in the chest or back may be due to pleurisy, pressure on nerves, or metastases in the vertebral column. *Pleural effusion* is common and is due to carcinomatous involvement of the pleura. The fluid is often blood-stained, reaccumulates rapidly after removal, and may contain clumps of tumor cells. There may be *pressure* on the esophagus, trachea, and recurrent laryngeal nerve with corresponding symptoms. *Fever* and *leucocytosis* may be due to occlusion of a bronchus and the accumulation of purulent material in the resulting bronchiectatic cavity.

**ADENOMA OF BRONCHUS.**—This rather uncommon tumor is remarkable for its long duration punctuated by repeated hemorrhages. Thus in a case of mine there were hemorrhages, sometimes copious, over a period of twenty-five years. The tumor is usually an adenomatous polyp growing in a main bronchus and causing obstruction of the lumen as well as hemorrhage. It may project on the surface, producing bronchial obstruction and forming a striking picture when seen with the bronchoscope. In other cases there is little to be seen on the surface, but there may be a large tumor growing into the lobe, a fact which emphasizes the necessity of lobectomy. Microscopically it consists of epithelial cells strikingly uniform in type, and usually forming solid masses reminiscent of a carcinoid tumor (Fig. 236). The cells may occasionally be arranged around spaces in glandular formation. The origin of the tumor is a matter of dispute. It may arise from basal cells in the bronchial mucosa or even from epithelialized alveoli, which would explain the fact that there is often a distinct space between the tumor and the bronchial epithelium. Al-

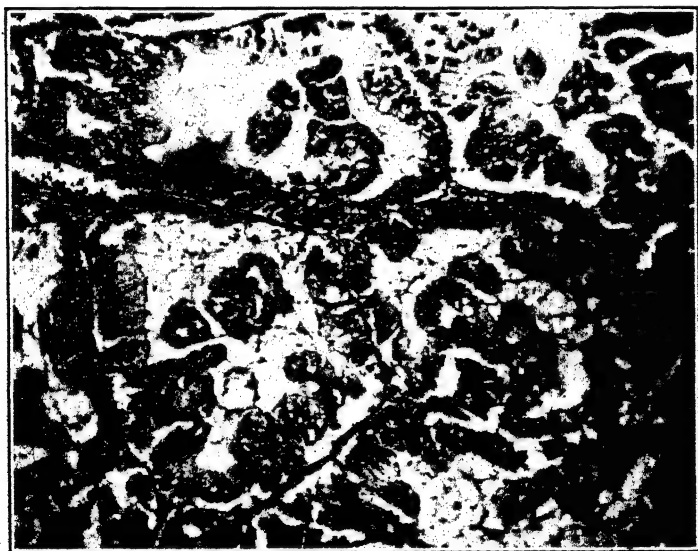


FIG. 237.—Pulmonary adenomatosis showing papillary processes and mucin in alveoli.

though the tumor is benign there is distinct invasion of the surrounding parenchyma and sometimes of the lymphatics. An adenoma may become carcinomatous, so that lobectomy is preferable to removal through the bronchoscope. It has been suggested that these tumors arise from embryonic bronchial buds which fail to develop and that they should be classed as "mixed tumors," similar to those which occur in the salivary glands (Womack and Graham).

**PULMONARY ADENOMATOSIS: Alveolar Cell Tumors.**—This rare condition consists of a proliferation of columnar epithelial cells, which usually produce mucin and line the alveolar spaces. Such a picture naturally suggests metastatic adenocarcinoma, so that a primary tumor either in the lung or elsewhere must first be excluded. The tumor may be of multiple nodular form or rarely diffuse. The nodular form is apt to be mistaken at autopsy for secondary carcinoma or miliary tuberculosis, whilst the diffuse form resembles the gray hepatization of lobar pneumonia. The cut



surface has a glairy mucoid appearance owing to the mucin which can be squeezed out. The microscopic appearance has already been indicated. Papillary processes are common and the alveoli are filled with mucin (Fig. 237). The finding of poly-poid processes of mucin-filled cells in the sputum is pathognomonic. Dense pleural adhesions are common. In about 25 per cent of cases there are metastases in the regional lymph nodes and there may be extension to distant organs. These are examples of malignant adenomatosis or alveolar cell carcinoma. Even in the cases which do not metastasize the condition may prove fatal because of the widespread replacement of alveoli with functional capacity. The proliferating cells appear to be derived from alveolar epithelium, although some writers believe that the origin is from the epithelium of the bronchioles. An infectious pneumonia of sheep known as jaagsiekte, possibly due to a virus, presents a similar microscopic picture.

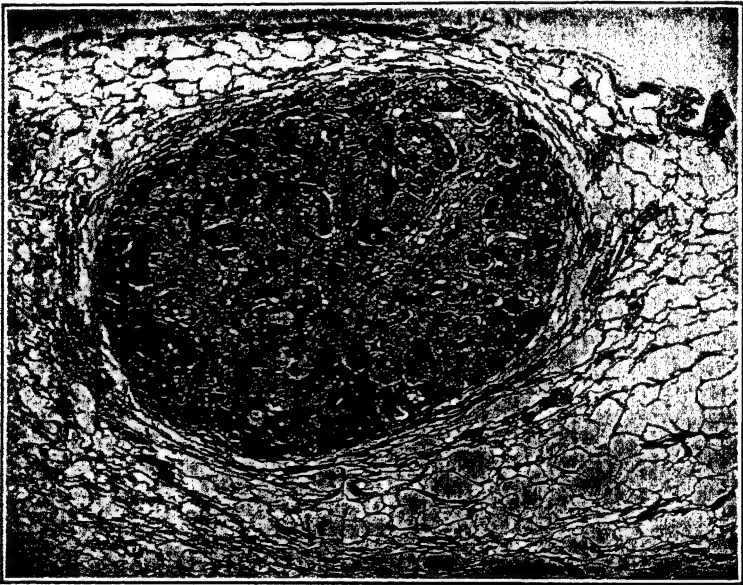


Fig. 238.—Secondary carcinoma of lung lying just under the pleura.  $\times 12$ .

**HEMANGIOMA.**—This is a rare tumor of the lung. It is really an arteriovenous fistula, an abnormal communication between arteries and veins. It can be diagnosed clinically and removed by operation, the chief features being increased blood volume, polycythemia, cyanosis, and clubbing of the fingers and toes. It will be seen that the clinical picture may easily be confused with that of congenital heart disease. The presence of a shadow in the x-ray film of the lung and the absence of heart murmurs are features suggestive of pulmonary hemangioma.

**HAMARTOMA.**—This is a small benign lesion of the lung situated at the periphery, usually symptomless and picked up in a routine radiological examination when it may arouse a suspicion of a more serious condition. A hamartoma (*hamartion*, a bodily defect), seen also in the kidney, is a developmental anomaly, well circumscribed, and consisting of the normal constituents of the part arranged in a jumbled and confused manner. Here it is composed principally of cartilage, often calcified, sometimes ossified, together with fat, fibrous tissue, muscle and gland-like struc-

tures. It may be presumed to originate as a faulty development of a bronchial anlage.

**PANCOAST'S SYNDROME.**—This is a clinical syndrome characterized by pain about the shoulder and down the arm, Horner's syndrome, local destruction of the first two or three ribs, atrophy of the muscles of the hand, and a roentgen-ray shadow at the extreme apex. Pancoast suggested the name of superior pulmonary sulcus tumor, but it is better called Pancoast's syndrome. Most of these cases are examples of apical bronchogenic carcinoma pressing on the brachial plexus and the sympathetic cervical chain, but without symptoms or signs of pulmonary disease. In a few instances the lesion may be an epidermal carcinoma arising from embryonal remains rather than any adjacent normal structure.

**Secondary Tumors.**—Secondary tumors of the lung are very common. Carcinoma may reach the lung by the blood stream or *via* the lymphatics (cancer of the breast). Many nodules are scattered through one or both lungs, and sometimes these nodules may be miliary in type. Microscopic clumps of tumor cells may be found where no gross tumor can be detected. In some cases the nodules are entirely subpleural, none being found in the substance of the lung (Fig. 238). Sarcoma of bone has a special tendency to metastasize to the lungs. Chorionepithelioma has the intensely hemorrhagic character of the primary tumor in the uterus.

## MEDIASTINAL TUMORS AND CYSTS

The mediastinum is a complex structure containing a great variety of tissues. It is natural that an equal number of tumors have been reported. The primary tumors may be in the anterior or the posterior mediastinum. By and large, the anterior mediastinal tumors are teratomas; the posterior group are neurogenic tumors.

**NEUROGENIC TUMORS.**—These tumors, which arise from the posterior roots of the spinal nerves, may be neurofibromas or ganglioneuromas. The great majority of the neurofibromas are benign and are picked up on routine mass x-ray examinations, but if they are left long enough they tend to become malignant. The neurofibroma, arising from the posterior nerve roots, grows forward pushing the parietal pleura in front of it, but it may grow backward through an intervertebral foramen and press on the spinal cord. This is the so-called dumb-bell tumor. The palisading of the nuclei or the whorled arrangement of the fusiform cells is characteristic of neurofibroma. When the tumor becomes malignant the growth is more disorderly and mitoses are frequent. The *ganglioneuroma*, more common in children, arises from sympathetic ganglia. It is a benign tumor composed of large adult ganglion cells with an admixture of small embryonal nerve cells. Neurogenic tumors are often symptomless, but they may give rise to root pain.

**TERATOID TUMORS.**—Developmental tumors, solid or cystic, are confined to the anterior mediastinum. They are likely to be discovered in adolescence or early adult life. The solid tumors are called teratomas, the cysts are dermoids. The teratomas are composed of a variety of structures, whilst the dermoids are cysts with ectodermal and mesodermal tissues, *i.e.*, epithelium, glands, hair, cartilage, bone and teeth. No really satisfying explanation has ever been given for the occurrence of teratoid tumors and cysts in the mediastinum. The solid tumors may become malignant developing into an epidermoid carcinoma or adenocarcinoma. Cough is the most constant symptom, though there may be pain and dyspnea. The sputum may be blood-streaked. Expectoration of hair, known as trichoptysis, is

the one pathognomonic symptom, although complaints by the patient of this occurrence have often been received with amused scepticism and incredulity. A circumscribed shadow is seen in the anterior mediastinum in the x-ray film, and the presence of teeth is pathognomonic.

**MEDIASTINAL CYSTS.**—Cysts, other than those of the teratoid group, never become malignant. They may be bronchial, esophageal, gastric, enteric, or pericardial in origin. They occur in the posterior mediastinum, with the exception of pericardial cysts, and are probably formed by a pinching off of a small bud of the bronchial tree.

The *bronchial* or *bronchiogenic cyst* is usually situated in the posterior part of the superior mediastinum at the bifurcation of the trachea or attached to a large bronchus. The wall consists of the normal constituents of the bronchial wall, and the cyst is lined by ciliated pseudostratified columnar epithelium. The esophageal cyst is lined by squamous stratified epithelium. *Gastric cysts* usually occur in young children; the wall is lined by gastric mucosa, and the contents are strongly acid. A peptic ulcer is liable to develop, which erodes the trachea and gives rise to hemoptysis. *Enteric cysts* are the rarest variety. They are lined by intestinal mucosa.

The *pericardial celomic cyst* arises in the course of development of the pericardial cavity, and is situated in the anterior mediastinum, usually at the cardiophrenic angle. The lining is a single layer of flattened cells, and the contents are so clear and limpid that the lesion has been given the poetic name of "spring-water cyst." There are usually no symptoms.

**LYMPH NODE TUMORS.**—These form the largest group of mediastinal tumors, and are situated in the anterior mediastinum. They may be primary or secondary. Tumors of the lymph nodes are discussed in Chapter 29, so that they will not be considered here.

## THE PLEURA

### PLEURISY

Inflammation of the pleura, pleuritis, or pleurisy must be much commoner than clinical observation would indicate, because adhesions due to a former pleurisy are among the commonest of postmortem findings. Pleurisy may be serofibrinous or purulent, the latter being usually known as empyema. The common causal organisms are pneumococcus, streptococcus and the tubercle bacillus.

**Serofibrinous Pleurisy.**—The exudate may be mainly fibrin (Fig. 239), the serous effusion being negligible or undetectable clinically. This is known as dry or fibrinous pleurisy. When the exudate is abundant the condition is called pleurisy with effusion. Pleurisy may be secondary to such pulmonary conditions as pneumonia, tuberculosis, carcinoma, and infarct, or to a neighborhood infection such as pericarditis, periostitis of the rib, or peritonitis. In such cases it is likely to be of the dry variety. Or it may appear to be a primary pleural condition, either dry or with effusion. These cases are almost all tuberculous in nature. The infection is not strictly primary, but probably begins in a subpleural focus in the lung from which it spreads to the pleura, both lesions subsequently becoming healed.

**LESIONS.**—The fibrinous exudate may be so thin as merely to dull the luster of the membrane or so thick that it can be peeled off in layers. Both parietal and visceral layers are involved, and stringy fibrinous ad-

hesions pass between the two layers and also between the lobes. Later these may become converted into permanent fibrous adhesions, and in extreme cases the entire cavity may be obliterated.

The fluid exudate may be very small in amount, as in the dry form, or it may fill the entire cavity. The fluid is clear or opalescent, depending on the number of cells it contains. When the fluid is withdrawn a jelly-like clot forms, owing to the high fibrinogen content. Hemorrhagic effusion indicates malignancy. When the effusion is abundant the lung is collapsed, the heart pushed over to the other side, the diaphragm pushed down, and the intercostal spaces widened.



FIG. 239.—Pleurisy showing fibrinous exudate.  $\times 130$ .



FIG. 240.—Subpleural abscess about to rupture. Rupture of such an abscess is certain to be followed by empyema.

**EMPYEMA.**—Purulent pleurisy is usually secondary to infection in the lung, sometimes to spread of infection from other organs—such as the pericardium, chest wall, or peritoneum. Pneumococcal empyema complicates lobar pneumonia in a small proportion of cases (2 to 5 per cent). Streptococcal empyemas are often due to rupture of a small subpleural abscess which floods the pleural cavity with the massive dose of organisms needed to produce suppuration (Fig. 240).

The *pleura* is covered by a layer of inflammatory exudate, which is much thicker than in the other two forms of pleurisy. This thick layer covers the parietal as well as the visceral layer, so that an exploring needle may have to be pushed in a long way before it encounters pus. In course of time the exudate becomes converted into fibrous tissue (Fig. 241) and

the lung may be bound down to such an extent that it fails to expand when the pus is evacuated. Very dense adhesions are likely to be formed.

The *lung* is collapsed to a degree depending on the amount of the fluid. In extreme cases it is flattened against the mediastinum and the posterior chest wall. Pressure of the pus may lead to necrosis and destruction of the lung at the seat of pressure. In long-standing cases there may be a diffuse fibrosis of the lung which combines with the adhesions and the pleural exudate to prevent expansion.

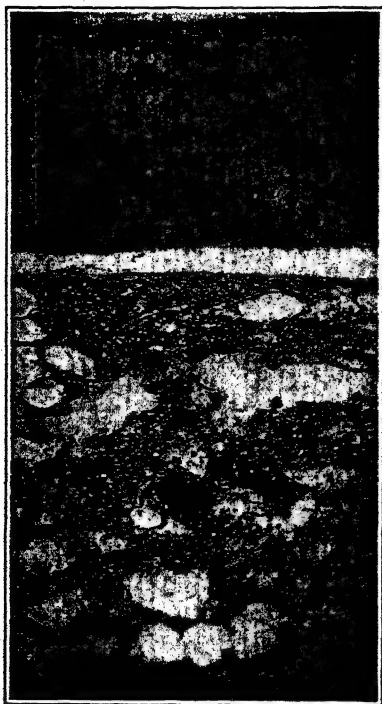


FIG. 241.—Greatly thickened pleura.  
× 40.

**THE RELATION OF SYMPTOMS TO LESIONS.**—The symptoms of the various forms of pleurisy are very similar. *Pain* in the side made worse by breathing is the most characteristic symptom. It is not caused by friction of the inflamed and roughened surfaces as is commonly supposed, for the friction rub may still be heard after the pain has ceased, and pleural pain may come on after pneumothorax. Like so many other pains it is due to tension, the inflamed and acutely sensitive parietal pleura being stretched every time the patient takes a deep breath. The visceral pleura is insensitive and so can take no part in producing the pain. Strapping of the chest relieves the pain by preventing the stretching of the parietal pleura; it does not prevent the friction. The pain disappears with the onset of effusion, because the fluid serves as a splint to immobilize the lower ribs. The *friction rub* is heard as long as the roughened surfaces are rubbing against one another; it disappears when the surfaces are separated by effusion.

## HYDROTHORAX

Hydrothorax is a fluid transudate, as opposed to an inflammatory exudate, in the pleural cavity. The watery fluid has a specific gravity below 1.018 and protein content below 4 per cent. It is a part of cardiac or renal edema. For some reason hydrothorax due to cardiac disease is usually right-sided. This may possibly be due to pressure of the dilated right auricular appendix on the pulmonary veins on that side, but it must be admitted that that explanation sounds rather far-fetched. In renal edema the pleural effusion is usually bilateral, and if it happens to be unilateral it is as common on the left as on the right.

**HEMORRHAGIC PLEURAL FLUID.**—*Hemothorax* is a condition in which blood is poured into the pleural cavity as the result of rupture of an aortic aneurism, fractured ribs, wounds of the chest, etc. In *hemorrhagic pleurisy* there is hemorrhage

into a preëxisting pleural effusion, so that the fluid is watery and bloody but not pure blood. This condition is usually due to carcinoma of the lung, either primary or secondary.

**CHYLOTHORAX.**—A milky fluid in the pleural cavity may be chyle, chyloform or pseudochyloous. True *chyle* is due to rupture or obstruction of the thoracic duct by trauma, malignant disease, tuberculosis or filaria. *Chyloform* fluids, which closely resemble chyloous fluid, are milky due to the presence of fine, fat droplets derived from fatty degeneration of cells in cancer of the lung or tuberculosis. A *pseudo-chyloous* fluid does not contain fat, although it may have a milky appearance, which may be due to the presence of albuminous particles in fine subdivision.

## PNEUMOTHORAX

Pneumothorax is air or gas in the pleural cavity, but there is usually an accompanying serous or purulent effusion, so that the condition is really a hydropneumothorax or pyopneumothorax. There is normally a negative pressure in the pleural cavity, and when the cavity communicates with the lung or the outside air rushes in, the negative pressure falls to zero, and as the opening is often valvular a positive pressure may take its place.

Pneumothorax is usually due to rupture of a subpleural tuberculous cavity. Sometimes it is caused by the bursting of an emphysematous bulla. Rarely it may be associated with abscess or bronchiectasis. Laceration of the pleura from without and tearing of the lung by a fractured rib are uncommon causes. Much more rare are perforation of the esophagus and rupture of an ulcer or cancer of the stomach through the diaphragm. There remains a small group of cases of spontaneous pneumothorax, in which the condition suddenly develops without any obvious cause. Some of these may be due to rupture of an emphysematous vesicle.

**SYMPTOMS.**—The onset is often sudden with severe pain in the side and great dyspnea, or it may be quite gradual. The affected side is enlarged and immobile, with lack of vocal fremitus, hyper-resonance, absence of breath sounds, and the characteristically echoing coin sound. When the patient is shaken the Hippocratic succussion splash may be heard in some cases.

**LESIONS.**—The air should be demonstrated before the chest is opened at autopsy. A needle may be pushed through the chest wall and the issuing gas may blow out a match. Or the skin may be reflected, and a small cup made in the intercostal muscles in which water is placed. When the pleura is punctured at this point bubbles of air appear in the water. When the chest is opened fluid will usually be found, which may be serous but is more often purulent (pyopneumothorax). The lung is collapsed, forming a small mass in the region of the hilus. The heart is pushed over to the opposite side and the diaphragm pushed down so that its under surface may become convex and the edge of the liver is far below the costal margin.

**THE RELATION OF SYMPTOMS TO LESIONS.**—The abrupt onset is due to the air suddenly rushing into a cavity where there is a negative pressure. The pain is caused by stretching of the parietal pleura. The enlargement and immobility of the affected side, hyper-resonance, and coin sound are due to the air which fills the pleural cavity. The dyspnea, lack of vocal fremitus, and absence of breath sounds are caused by collapse of the lung, and the succussion splash is caused by the movement of the fluid. The roentgen-ray picture is highly characteristic (air, fluid, and collapsed lung).

## TUMORS OF THE PLEURA

Tumors of the pleura may be primary or secondary. Primary tumors are rare; secondary tumors (carcinoma) are fairly common.

**PRIMARY TUMORS.**—These may be divided into two main groups, the localized and the diffuse. The *localized* tumors are of many histological types, but they have one characteristic in common; they arise from the tissues beneath the surface lining, whereas the diffuse tumors arise from this layer of cells. The localized tumors may grow from the parietal or visceral pleura. The most important member is the so-called giant sarcoma of the visceral pleura, which is of very slow growth and does not infiltrate nor metastasize, so that by the time it is discovered it may attain an enormous size and fill the entire pleural cavity. It has the microscopic structure of a fibrosarcoma, but does not behave like a malignant growth.

The *diffuse* tumor arises from the surface lining cells, and is commonly known as an endothelioma. It would be better called a *mesothelioma*, as the surface cells are mesothelial in character, the lining of the pleural cavity being derived from the coelomic epithelium, which in turn is developed by a splitting of the mesoderm. The tumor may present characteristics of either epithelial or connective tissue, due to the varied potentialities of the mesothelial cells. It causes a diffuse thickening of the pleura which may extend over a considerable area or even the entire lung and may be over 1 cm. in depth. Both layers of the pleura may be involved. Pleural effusion is common, at first serous and later hemorrhagic. *Microscopically* the tumor consists of large spherical cells arranged in solid masses and columns, often within the lumen of lymphatics; they may have a definite glandular formation as in an adenocarcinoma. The stroma is usually fibrous and abundant.

**SECONDARY CARCINOMA.**—In secondary cancer of the lung the pleura may be involved, but not infrequently the pleura is studded with small tumors although none are to be seen in the lung. Sometimes a network of lymphatics is outlined as a series of white lines due to permeation by carcinoma cells. The primary tumor is usually in the breast.

#### ADDITIONAL READING

- Adenoma of Bronchus.** DELARUE: *J. Thoracic Surg.*, 21, 535, 1951. FRIED: *Bronchio-genic Carcinoma and Adenoma. With Chapter on Mediastinal Tumors.* Baltimore, Williams & Wilkins, 1948. (a) p. 39. (b) p. 57. (c) p. 192. (d) p. 258. GRAHAM AND WOMACK: *J. Thoracic Surg.*, 1945, 14, 106. HOLLEY: *Military Surgeon*, 1946, 99, 528. WESSLER AND RABIN: *Am. J. Med. Sci.*, 1932, 183, 164. WOMACK AND GRAHAM: *Arch. Path.*, 1938, 26, 165.
- Alveolar Hyaline Membrane.** FARBER AND WILSON: *Arch. Path.*, 1932, 14, 437, 450.
- Alveolar Phagocytes.** FOOT: *Am. J. Path.*, 1927, 3, 413. GARDNER AND SMITH: *Am. J. Path.*, 1927, 3, 445. MACKLIN: *Trans. Roy. Soc. Canada*, 1946, ser. 3, sec. V., 40, 93. MARSHALL: *J. Path. & Bact.*, 1946, 58, 729. PERMAR: *J. Med. Res.*, 1923, 44, 27.
- Amniotic Fluid Embolism.** SCHENKEN, *et al.*: *Am. J. Clin. Path.*, 1950, 20, 147. STEINER AND LUSHBAUGH: *J. A. M. A.*, 1941, 117, 1245, 1340.
- Anthraxosis.** BELT: *Med. Res. Council, Spec. Report Series*, No. 243, 1942. CUMMINS AND SLADDEN: *J. Path. and Bact.*, 1930, 33, 1095.
- Apical Scars.** DAYSON AND SUSMAN: *J. Path. and Bact.*, 1937, 45, 597. MACMILLAN: *Arch. Path.*, 1949, 48, 377. MEDLAR: *Am. Rev. Tuberc.*, 1947, 55, 511.
- Asbestosis.** COOKE: *Brit. Med. J.*, 1927, 2, 1024. LYNCH AND SMITH: *J. A. M. A.*, 1930, 95, 659.
- Aspergillosis.** DONALDSON, *et al.*: *J. Lab. and Clin. Med.*, 1942, 27, 740. HETHERINGTON: *Am. Rev. Tuberc.*, 1943, 47, 107.
- Asthma.** CHRISTOPHERSON: *Lancet*, 1933, 1, 11. HUBER AND KOESSLER: *Arch. Int. Med.*, 1922, 30, 689. MACDONALD: *Ann. Int. Med.*, 1932, 6, 253. TOWEY, *et al.*: *J. A. M. A.*, 1932, 99, 453.
- Atelectasis.** ALLEN AND ADAMS: *Surg., Gynec. and Obst.*, 1930, 50, 385. CORTILLOS AND BIRNBAUM: *Arch. Surg.*, 1929, 18, 190.
- Barrite Fibrosis.** SHAVER: *Radiology*, 1948, 50, 760. WYATT AND RIDDELL: *Am. J. Path.*, 1949, 25, 447.

- Beryllium Pneumonitis.** AGATE: *Lancet*, 1948, 2, 530. CHESNER: *Ann. Int. Med.*, 1950, 32, 1028. DUTRA: *Am. J. Path.*, 1948, 24, 1137. VAN ORDSTRAND, *et al.*: *J. A. M. A.*, 1945, 129, 1084.
- Bronchiectasis.** LIEBOW, *et al.*: *Am. J. Path.*, 1949, 25, 211. MALLORY: *New Eng. J. Med.*, 1947, 237, 795. ERB: *Arch. Path.*, 1933, 15, 357. ROBINSON, *Brit. J. Surg.*, 1933, 21, 302. SMITH: *Arch. Surg.*, 1930, 21, 1173. WARNER: *Quart. J. Med.*, 1934, 3, 401.
- Bronchiolitis Fibrosa Obliterans.** LADUE: *Arch. Int. Med.*, 1941, 68, 663.
- Bronchogenic Carcinoma.** BARNARD: *J. Path. and Bact.*, 1926, 29, 241. DOLL AND HILL: *Brit. M. J.*, 1950, 2, 739. *Brit. Med. J.*, 1952, 2, 1271. DUNGAL: *Lancet*, 1950, 2, 245. FRIED: *Bronchogenic Carcinoma*, Baltimore, 1948. GRAHAM: *New Eng. J. Med.*, 1951, 245, 389. HERBUT: *Am. J. Path.*, 1944, 20, 911; *Arch. Path.*, 1946, 41, 175. KENNAWAY AND KENNAWAY: *Brit. J. Cancer*, 1947, 1, 260. OCHSNER, *et al.*: *J. A. M. A.*, 1952, 148, 691. PASSEY AND HOLMES: *Quart. J. Med.*, 1935, 4, 321. PEERY: *Arch. Path.*, 1940, 29, 625. PIRCHAN AND SIKL: *Am. J. Cancer*, 1932, 16, 681. SIMONS: *Primary Carcinoma of the Lung*, Chicago, 1937. STEINER: *Arch. Path.*, 1944, 37, 185. TANNER AND GORDON: *Am. J. Path.*, 1952, 28, 953. WELLER: *Arch. Path.*, 1929, 7, 478; *J. Cancer Res.*, 1929, 13, 218. WYNDER AND GRAHAM: *J. A. M. A.*, 1950, 143, 329.
- Chronic Disseminating Tuberculosis.** KAYNE, *et al.*: *Pulmonary Tuberculosis*, London, 1939, p. 103. MILLER: *Am. Rev. Tuberc.*, 1934, 29, 489.
- Cigarettes and Lung Cancer.** DOLL AND HILL: *Brit. M. J.*, 1950, 2, 739. WYNDER AND GRAHAM: *J. A. M. A.*, 1950, 143, 329. DUNGAL: *Lancet*, 1950, 2, 254.
- Congenital Cystic Lung.** FLEMING: *Arch. Dis. Child.*, 1934, 9, 201. KOONTZ: *Bull. Johns Hopkins Hosp.*, 1925, 37, 340. MILLER: *Arch. Surg.*, 1926, 12, 392.
- Cytologic Diagnosis of Lung Cancer.** FARBER, *et al.*: *J. A. M. A.*, 1950, 144, 1.
- Differentiation of Fetal Lung.** WADDELL: *Arch. Path.*, 1949, 47, 227.
- Emphysema.** HARTROFT: *Am. J. Path.*, 1945, 21, 889. LIEBOW: *Am. J. Path.*, 1953, 29, 251.
- Epituberculosis.** HUTCHISON: *Quart. J. Med.*, 1949, 18, 21. OPPENHEIMER: *Bull. Johns Hopkins Hosp.*, 1935, 57, 247.
- Fungous Diseases of Lungs.** BASS: *J. A. M. A.*, 1950, 143, 1041.
- Giant-cell Pneumonia.** CHOWN: *Am. J. Dis. Child.*, 1939, 57, 489. PINKERTON, *et al.*: *Am. J. Path.*, 1945, 21, 1.
- Giant-cell Pneumonitis.** McMILLAN: *Am. J. Path.*, 1947, 23, 995
- Graphite Pneumoconiosis.** JAFFE: *Am. J. Path.*, 1951, 27, 909.
- Hamartoma.** GOLDSWORTHY: *J. Path. & Bact.*, 1934, 39, 291. McDONALD, HARRINGTON AND CLAGETT: *J. Thoracic Surg.*, 1945, 14, 128. WHITESIDE: *Can. Med. Ass.*, 1950, 63, 383.
- Healing of Tuberculous Cavities.** PAGEL AND SIMMONDS: *Am. J. Med. Sci.*, 1942, 203, 177.
- Hemangioma of Lung.** SMITH AND HORTON: *Am. Heart J.*, 1939, 18, 589.
- Idiopathic Hemosiderosis.** McLEITCHIE AND COLPITTS: *Can. Med. Ass. J.*, 1949, 61, 129. WYLLIE, *et al.*: *Quart. J. Med.*, 1948, 17, 25.
- Influenza.** OPIE: *Arch. Path.*, 1928, 5, 285. PARKER, *et al.*: *Am. J. Path.*, 1946, 22, 797.
- Interstitial Emphysema.** MACKLIN AND MACKLIN: *Medicine*, 1944, 23, 281.
- Lipoid Pneumonia.** GRAEF: *Arch. Path.*, 1939, 28, 613. LAUGHLIN: *Am. J. Path.*, 1925, 1, 407. WOLMAN AND BAYARD: *Am. J. Med. Sci.*, 1941, 202, 542.
- Lobar Pneumonia.** GASKELL: *J. Path. and Bact.*, 1925, 28, 427. LOOSLI: *J. Exper. Med.*, 1942, 75, 657; 76, 79. LUNSGAARD: *Medicine*, 1925, 4, 345. ROBERTSON AND UHLEY: *J. Clin. Invest.*, 1936, 15, 115. ROBERTSON, *et al.*: *J. Clin. Invest.*, 1933, 12, 467. WOOD: *J. Exper. Med.*, 1941, 73, 201; 1946, 84, 365, 377, 387.
- Löffler's Syndrome.** BAYLEY, *et al.*: *Arch. Path.*, 1945, 40, 376.
- Malignant Granuloma of Nose.** HARGROVE, FODDEN AND RHODES: *Lancet*, 1946, 2, 596. McCART: *Can. Med. Ass.*, 1950, 63, 357.
- Mediastinal Cysts.** LAIPPLY: *Arch. Path.*, 1945, 39, 153.
- Mediastinal Teratoma.** HOUGHTON: *Am. J. Path.*, 1936, 12, 349.



- Mediastinal Tumors.** BLADES: *Ann. Surg.*, 1946, **123**, 749. HAAGENSEN: *Am. J. Cancer*, 1932, **16**, 723. LAIPPY: *Arch. Path.*, 1945, **39**, 153. LILLIE, McDONALD AND CLAGETT: *J. Thoracic Surg.*, 1950, **20**, 494.
- Mucosal Respiratory Syndrome.** STANTON AND WARNER: *Can. Med. Ass. J.*, 1945, **53**, 427. STEVENS AND JOHNSON: *Am. J. Dis. Child.*, 1922, **24**, 526.
- Non-tuberculous Pulmonary Calcification.** LUMSDEN, *et al.*: *Am. J. Pub. Health.*, 1939, **29**, 25. PALMER: *Pub. Health Rep.*, 1945, **60**, 513.
- Pleural Neoplasms.** KLEMPERER AND RABIN: *Arch. Path.*, 1931, **11**, 385.
- Pneumonia in New-born.** MACGREGOR: *Arch. Dis. Child.*, 1939, **14**, 323.
- Primary Atypical Pneumonia.** ROBERTSON AND MORLE: *Brit. Med. J.*, 1951, **2**, 994.
- Pulmonary Adenomatosis.** HERBUT: *Am. J. Path.*, 1944, **20**, 911. NEUBUERGER AND GEEVER: *Arch. Path.*, 1942, **33**, 551. SIMON: *Am. J. Path.*, 1947, **23**, 413. SWAN: *Arch. Path.*, 1949, **47**, 517.
- Pulmonary Embolism.** BELT: *Am. J. Path.*, 1934, **10**, 129. KARSNER AND ASH: *J. Med. Res.*, 1912, **27**, 205.
- Pulmonary Fibrosis of Uncertain Nature.** BELT: *Frankfurt. Ztschr. f. Path.*, 1931, **42**, 170. HAMMAN AND RICH: *Bull. Johns Hopkins Hosp.*, 1944, **74**, 177. MALLORY: *Radiology*, 1948, **51**, 468. PEABODY, *et al.*: *J. Thor. Surg.*, 1951, **21**, 519.
- Pulmonary Fibrosis Secondary to Pneumonia.** AUERBACK, MIMS AND GOODPASTURE: *Am. J. Path.*, 1952, **28**, 69.
- Pulmonary Infarct.** CASTLEMAN: *Arch. Path.*, 1940, **30**, 130.
- Pulmonary Lesions in the New-born.** FARBER AND SWEET: *Am. J. Dis. Child.*, 1931, **42**, 1372. FARBER AND WILSON: *Am. J. Dis. Child.*, 1933, **46**, 572, 590. WARWICK: *Am. J. Med. Sci.*, 1934, **187**, 253.
- Pulmonary Tuberculosis.** DOCK: *Am. Rev. Tuberc.*, 1946, **53**, 297. KAYNE: *et al.*: *Pulmonary Tuberculosis*, London, 1939. RICH: *The Pathogenesis of Tuberculosis*, Springfield, 1944. SWEANT: *Age Morphology of Primary Tuberculosis*, Baltimore, 1941. TERPLAN: *Am. Rev. Tuberc. (Suppl.)*, 1940, **42**, 1.
- Pulmonary Tuberculosis in Children.** BLACKLOCK: *Great Brit. Med. Res. Council, Spec. Rep. Series*, No. 172, London, 1932. CHOWN AND MEDOVY: *Can. Med. Ass. J.*, 1933, **29**, 364. GHON: *Der primäre Lungenherd bei der Tuberculose der Kinder*, Berlin, 1912.
- Radiation Pneumonitis.** WARREN AND GATES: *Arch. Path.*, 1940, **30**, 440.
- Sequestration of Lung.** PRYCE, *et al.*: *Brit. J. Surg.*, 1947, **35**, 18.
- Silicosis.** AMOR: *An X-Ray Atlas of Silicosis*, Bristol, 1943. BELT, *et al.*: *J. Path. and Bact.*, 1940, **51**, 263. CUMMINGS AND SLADDEN: *J. Path. and Bact.*, 1930, **33**, 1095. HALE: *Brit. J. Tuberc.*, 1945, **39**, 91. KETTLE: *Brit. Med. J.*, 1932, **2**, 281; *Proc. Roy. Soc. Med.*, 1930, **24**, 79. LYNCH: *Am. J. Path.*, 1942, **18**, 313.
- Structure of Fetal Lung.** BERNARD AND DAY: *J. Path. and Bact.*, 1937, **45**, 67. HAM AND BALDWIN: *Anat. Rec.*, 1941, **81**, 363.
- Superior Pulmonary Sulcus Tumor.** MORRIS AND HARKEN: *Ann. Surg.*, 1940, **112**, 1.
- Virus Pneumonia.** ADAMS: *J. A. M. A.*, 1941, **116**, 925. WEIR AND HORSFALL: *J. Exper. Med.*, 1940, **72**, 595.

## Chapter

# 18

## THE MOUTH, NECK, AND ESOPHAGUS

### THE LIPS

THE important lesions of the lips are cancer, primary syphilis, and angioma.

**Carcinoma.**—Cancer of the lip is one of the commonest forms of malignant disease. But it is only common in one sex (male) and in one lip (lower). It is quite rare in women and in the upper lip. The high incidence in the lower lip may be attributed to its being much more exposed to irritation (biting, action of actinic rays, etc.). The disease is commonly preceded by some lesion caused by chronic irritation such as fissures, abrasions due to jagged teeth, a patch of seborrhea or leukoplakia, etc. The prognosis is excellent, whether treated by surgical removal or radiotherapy.

The disease begins as a local thickening and induration. If growth is mainly toward the surface a warty nodule is formed which soon becomes ulcerated. If growth is deep the chief lesion is a deep-seated induration, and there may be no surface tumor or ulceration for a considerable time. When an ulcer does form it has the usual hard raised edges of a malignant sore.

*Microscopically* the tumor is an epidermoid carcinoma. Most of the cases belong to Grades 1 and 2, and a fair number to Grade 3, but I have never seen a case of Grade 4. It may be pointed out here that a convenient practical method of grouping the tumors of the oral cavity from the point of view of malignancy is as follows: (1) tumors from lips to teeth—mostly low grade; (2) tumors from teeth to back of tongue—increasing in malignancy as we pass back; (3) tumors of pharynx—high grade of malignancy.

**SPREAD.**—The spread, which is very slow in the lower grade tumors, is by lymphatics, seldom by the blood stream. The malignant ulcer may destroy the lip, the skin of the chin, and finally involve the mandible. The submaxillary lymph nodes are involved from the lateral part of the lip, the submental from the central part, but the corresponding salivary glands are seldom involved. The tumor cells may then spread to all the superior cervical lymph nodes, both superficial and deep, but as there is no direct connection between the lip and the inferior cervical and supraclavicular groups, these nodes are seldom involved until very late in the disease.

**SYPHILIS.**—A primary chancre of the lip may be on either lip, but is usually on the upper. It is usually caused by kissing, but an infant may be infected through

being suckled by a syphilitic wet-nurse. The lesion begins as a hard nodule which may ulcerate and develop into a typical chancre. There is the usual regional lymph node involvement, the submental and submaxillary nodes becoming enlarged and hard. When ulceration occurs spirochetes are readily demonstrated by the dark-field method.

**ANGIOMA.**—These are not uncommon tumors in children and are probably congenital. Both hemangioma and lymphangioma occur and cause a characteristic diffuse enlargement of the lip. A hemangioma has a bluish color, but a lymphangioma is colorless.

## THE MOUTH

**TONSILLITIS.**—Acute tonsillitis may be follicular or parenchymatous. *Follicular* tonsillitis is so called because the inflammation is confined to the lymph follicles surrounding the crypts. The tonsils are large and red, and the surface is covered with yellow spots of pus which can be wiped away. The *parenchymatous* form or *quinsy* is a diffuse inflammation involving the whole tonsil and spreading to the surrounding tissues. Quinsy is characterized by suppuration, swelling of the peritonsillar tissue and deviation of the uvula to one side. The cervical lymph nodes are enlarged and tender, for they also are inflamed. The *microscopic* picture is one of diffuse suppuration.

**DIPHTHERIA.**—The lesions of diphtheria are chiefly in the throat, on the tonsil, pharynx, and soft palate. The lesions are usually localized, taking the form of a gray patch of inflammatory exudate known as a false membrane, which is firmly adherent to the underlying tissue so that when it is removed it leaves a raw surface. *Microscopically* the gray patch is composed of fibrin threads and necrotic epithelium. The fibrin is interwoven with the necrotic cells, thus explaining the firmness with which the exudate is attached. Large numbers of diphtheria bacilli are present in the membrane.

**VINCENT'S ANGINA.**—This is a destructive lesion associated with the presence of two organisms, a long fusiform bacillus with pointed ends and a spirochete which stains faintly with ordinary aniline dyes. These Vincent organisms, as they may be called, are probably closely related. They are readily demonstrated in direct smears (not culture), where the spirochetes may form tangled masses. The lesion, which is usually on or near the tonsil, is at first necrotic, and when the slough has separated a large cavity may be left. Before adopting drastic local treatment of a necrotic gingivitis a leucocyte count should be done to exclude agranulocytic angina.

**SYPHILIS.**—*Secondary* lesions take the form of bilateral grayish-white patches (mucous patches) like the track of a snail, or superficial ulcers. These lesions may occur on the tonsils, soft palate, or buccal mucous membrane. *Tertiary* lesions are gummata which break down and leave deep, punched-out ulcers. This lesion is most often seen on the hard palate, where it causes perforation of the palate and regurgitation of food through the nose, but it may also occur on the tonsil and fauces.

**Carcinoma.**—Cancer of the mouth is similar to the much commoner cancer of the tongue and will be merely mentioned. It occurs in the lower rather than the upper oral cavity, chiefly on the floor of the mouth, the cheek and the mandible. The lesion is at first a localized thickening, but later becomes a deep excavated ulcer. *Leukoplakia* is a frequent precancerous lesion, often associated with a badly fitting dental plate. Also probably precancerous in character are degenerative mucous membrane changes found in the majority of mouth cancers. These are usually the result of a combination of avitaminosis with various forms of chronic

irritation, *e. g.*, tobacco, syphilis, and sepsis (Martin and Koop). Lack of vitamin B is the most frequent deficiency, and probably the most important from the point of view of carcinogenesis. Microscopically oral cancer is an epidermoid carcinoma, but of higher grade and much more serious than cancer of the lip.

## THE TONGUE

**INFLAMMATION.**—Glossitis or simple inflammation of the tongue may take the form of an acute diffuse inflammation or of ulcers. *Acute glossitis* is not a common condition. It may be caused by the sting of a bee, an infected wound, etc. There is rapid swelling of the tongue and suppuration, and the patient may be nearly choked before the pus is let out. *Simple ulcers* occur at the edge or tip of the tongue, and are often due to the irritation of a jagged tooth or badly-fitting plate. The ulcer is at first shallow and acute in type, but if the irritant is not removed it may become more chronic with indurated edges, and may eventually become malignant. Shallow painful ulcers, usually of short duration, often develop in the mouth and on the tongue as the result of constitutional disturbances. Some persons are particularly susceptible. The pathogenesis of these lesions is not clear; they are probably surface infections. The condition commonly called *chronic glossitis* is nearly always syphilitic, and will be described under that heading.

**SYPHILIS.**—A syphilitic lesion of the tongue may be primary, secondary or tertiary. A *primary chancre* presents the usual appearance of the hard sore. Spirochetes can be demonstrated by the dark-field. The induration of the lesion and the fact that lymph nodes in the floor of the mouth are enlarged and hard may easily lead to a mistaken diagnosis of carcinoma, a much commoner condition. The *secondary* lesions are mucous patches or shallow ulcers. They are swarming with spirochetes and are highly infectious. The *tertiary* lesions may take the form of an ulcer or a diffuse glossitis. A *syphilitic ulcer* is caused by the breaking down of a gumma and is usually situated on the dorsum of the tongue. It is liable to be mistaken for carcinoma, but it seldom shows the same degree of induration and the regional lymph nodes are not enlarged. *Syphilitic glossitis* causes an epithelial proliferation with the formation of lozenge-shaped white patches (leukoplakia) often separated by painful cracks and fissures. As carcinoma is apt to develop in one of the deep cracks, the lesion can be regarded as a precancerous one. Sometimes there is diffuse fibrosis which causes great enlargement of the tongue (syphilitic macroglossia).

**Carcinoma.**—Cancer of the tongue shows the same strong sex incidence as cancer of the lip, being quite rare in women. It seldom develops in a healthy tongue, being preceded by such precancerous conditions as chronic ulceration and syphilitic glossitis (leukoplakia, cracks, etc.). When a patient with a chronic ulcer on the dorsum of the tongue is found to have a positive Wassermann reaction, the case should be regarded as malignant until proved otherwise by biopsy. The tongue is divided into two portions by the V-shaped line of circumvallate papillæ, the anterior two-thirds and the posterior one-third. Cancer of the anterior two-thirds is epidermoid in type, usually of distinctly higher grade than cancer of the lip. The edge is the common site, but the tumors which develop on a syphilitic basis are often on the dorsum. Cancer of the posterior third is fortunately much rarer, for it is usually markedly malignant although at the same time markedly radio-sensitive. It is likely to be a high-grade epidermoid or occasionally a transitional-cell carcinoma. The *gross appearance* at first

presents merely a local induration; this may develop into a warty mass with early ulceration, but often the tumor takes a form of a deep infiltration and ulceration may be late. The malignant ulcer is characteristically hard with raised, indurated, rounded edges. Extensive necrosis, sloughing, destruction, and secondary infection constitute the finish of the picture. The *microscopic appearance* has already been indicated, *i. e.*, epidermoid or transitional-cell (posterior third). *Spread* is rapid, so that it is of the first importance not to temporize with a suspicious ulcer or indurated patch on



FIG. 242.—Tuberculosis of tongue not yet ulcerated.  $\times 90$ .

the tongue. Time should be measured here in days, whereas in a similar lesion of the lip it may be measured in weeks or even months. An immediate biopsy is imperative. The most important reasons for the rapid spread are: (1) the extremely rich lymphatic drainage of the tongue, (2) the constant muscular movements, and (3) the high grade of the tumor. Lymph spread takes place into the submental and submaxillary lymph nodes, into the superior and inferior deep cervical nodes, and even into the supraclavicular nodes. In tumors of the posterior third the upper deep cervical group on both sides of the neck may be involved. Blood spread to distant organs is comparatively rare.

**TUBERCULOSIS.**—For practical purposes tuberculosis of the tongue may be taken to be secondary to pulmonary tuberculosis. It is remarkable how uncommon a complication it is. The squamous epithelium evidently acts as an efficient protection against the countless tubercle bacilli which must pass over it in a case of active

phthisis. The lesion usually commences as an ulcer near the tip of the tongue with sinuous undermined edges, pale watery-looking granulations, and an absence of the induration characteristic of malignant disease. Nevertheless the condition is frequently mistaken for carcinoma. Sometimes it begins as a nodule which ulcerates later (Fig. 242).

**ULCERS OF THE TONGUE.**—It is evident that an ulcer of the tongue may be inflammatory (simple), malignant, syphilitic, or tuberculous. A *simple* ulcer occurs on the edge or tip, is shallow and inflamed, and is often associated with a sharp tooth or jagged plate. A *malignant* ulcer occurs on the edge or center, is peculiarly hard with raised edges, and may be associated with syphilitic glossitis and enlargement of

the regional lymph nodes. A *syphilitic* ulcer occurs on the dorsum, is serpiginous in outline, and is usually a tertiary lesion. A *tuberculous* ulcer occurs at the tip, has undermined edges without induration, and is secondary to pulmonary tuberculosis.

**INNOCENT TUMORS.**—*Angioma* forms a soft bluish mass in the tongue, and is usually congenital. *Lymphangioma* causes a diffuse congenital enlargement (macroglossia). *Dermoid cysts* may occur under the tongue. A *thyroglossal cyst* at the upper end of the thyroglossal duct may form a swelling at the base of the tongue.

## THE PHARYNX

Many of the lesions of the pharynx have already been discussed in connection with the mouth, but one or two remain to be considered.

**Retropharyngeal Abscess.**—Pus may be formed as the result of suppuration in the loose tissue between the posterior wall of the pharynx and the vertebral column. It usually occurs in children suffering from some debilitating illness, and comes on acutely with rigidity of the neck, pain on swallowing, loss of voice, and a tense bulging on the posterior wall of the pharynx indicating the presence of pus. In tuberculosis of the cervical spine a chronic (cold) abscess may form in the same situation. *Ludwig's angina* is an acute diffuse streptococcal cellulitis involving the neck and tongue as well as the structures at the back of the throat. It usually occurs as a complication of one of the streptococcal fevers such as scarlet fever or erysipelas. There is a brawny induration of the neck with pressure on the trachea and edema of the glottis. The condition usually proves fatal in the course of a few days.

**Tumors of the Pharynx.**—A malignant tumor of the pharynx is likely to be an epidermoid carcinoma, transitional-cell carcinoma, lympho-epithelioma or lymphosarcoma.

**EPIDERMOID CARCINOMA.**—This may commence in the pharyngeal wall, the tonsil, or the soft palate. It produces a characteristic induration and soon ulcerates, leading to great destruction of the deeper tissues with secondary infection and a very foul breath. The lymph nodes at the angle of the jaw become enlarged and hard. Willis has pointed out that invasion of the jugular vein is a fairly common occurrence in epidermoid carcinoma of the head and neck with visceral metastases, especially in the liver. Nasopharyngeal carcinoma is the second commonest cancer in South-East Asia, especially amongst the Chinese. *Cancer of the hypopharynx* (post-cricoid carcinoma) is confined almost exclusively to women. This is the only malignant tumor of the alimentary canal which has this sex incidence. It is often preceded over a number of years by a combination of dysphagia, dry atrophy of the pharyngeal mucosa, and hypochromic anemia (Plummer-Vinson syndrome). Both the anemia and the mucosal change have a dietetic iron-deficiency basis. The mucosal atrophy seems to act as a precancerous lesion. Adequate treatment of the anemia with iron may therefore prevent the onset of the cancer.

**Transitional-cell Carcinoma and Lympho-epithelioma.**—There is difference of opinion as to whether these tumors are separate entities or are variants of the same lesion. The gross character and the method of spread is similar,

so that they may be considered together. The tumor arises from epithelium covering lymphoid tissue, and originates in the nasopharynx, oropharynx and laryngopharynx (sinus pyriformis). Its chief characteristic is that the primary tumor, while still small and undetected, may give rise to large secondary growths in the cervical lymph nodes on both sides. The growth is centrifugal rather than centripetal. There is often invasion of the base of the skull with involvement of the cranial nerves, particularly the fifth and sixth. The growth may penetrate the cranial cavity. Secondary growths may occur in the lungs and liver at a later date. The tumor is markedly radio-sensitive, and the mass in the neck may melt away for a time. *Microscopically* the transitional-cell carcinoma is highly anaplastic, consisting of sheets of large pale cells showing numerous mitotic figures with no attempt at cornification. The lympho-epithelioma presents a similar picture, but in addition groups of lymphocytes are mingled with the epithelial cells, or they may be scattered more diffusely among these cells.

**LYMPHOSARCOMA.**—This may arise in the tonsil or in the lymphoid tissue of the naso-pharynx. The tonsillar cases are at first unilateral. The cervical and axillary lymph nodes are involved, and later the lymphoid tissue in the rest of the body. *Microscopically* the tumor may be of the lymphocytic or the reticulo-endothelial type.

## THE NECK

The *severe inflammations* of the neck (Ludwig's angina and retro-pharyngeal abscess) have already been considered. Boils and carbuncles are common on the back of the neck owing to the friction of the collar.

**Cysts.**—A cyst of the neck may be mesial or lateral. The former is a thyroglossal cyst, the latter may be a branchial cyst or a cystic lymphangioma.

**THYROGLOSSAL CYST.**—The thyroglossal duct is a vestigial structure which passes from the foramen cecum at the base of the tongue to the isthmus of the thyroid gland. If a portion of the duct remains unclosed a cyst is formed lined by columnar epithelium. Such a cyst must always be in the middle line. It is usually below the hyoid bone, but occasionally is at the base of the tongue.

**BRANCHIAL CYST.**—This is formed from an unclosed portion of a branchial cleft, usually the third, and is therefore at the level of the hyoid bone. If it arises from the second cleft it lies just below the mastoid process and projects into the mouth. The cyst is usually lined by columnar ciliated epithelium, but when quite superficial it is lined by stratified epithelium. The wall contains much lymphoid tissue. If the outer end of the cleft remains open the condition is a *branchial fistula*, which opens on the neck at the level of the angle of the jaw.

**CYSTIC LYMPHANGIOMA.**—The vessels of a lymphangioma may undergo marked dilatation so as to form a soft cystic swelling, usually in the anterior triangle of the neck, but sometimes in the axilla or on the chest wall. It is a congenital condition and is usually seen in children, tending to undergo spontaneous cure before adult life is reached. It is subject to recurring

attacks of inflammation which probably play a part in the cure by closing the vessels. It is known clinically as *cystic hygroma* (fluid tumor), and may attain a very large size.

**Tumors.**—Tumors of the neck may be primary or secondary. Primary tumors may be accessory thyroid tissue (considered in connection with the thyroid gland), lymphoblastoma, branchial cleft carcinoma, and carotid body tumor. Secondary tumors are examples of carcinoma. Salivary gland tumors are considered separately (see below).

**LYMPHOBLASTOMA.**—Enlargement of the cervical lymph nodes may be due to any member of the lymphoblastoma group, *i. e.*, lymphosarcoma, Hodgkin's disease, and lymphatic leukemia. The disease often commences in the cervical group involving first one and then both sides. Later the lymph nodes throughout the body become enlarged. In leukemia the blood shows the characteristic leukemic change.

**BRANCHIAL CLEFT CARCINOMA.**—This rare tumor arises from remnants of branchial cleft epithelium. It is very much commoner in males than females. The tumor forms a very hard mass which starts deep in the neck near the bifurcation of the common carotid artery and infiltrates the surrounding tissue. The growth is a squamous-cell carcinoma, but with little tendency to cornification or cell-nest formation.

**CAROTID BODY TUMOR.**—This is a firm, round, slowly-growing tumor in the bifurcation of the common carotid artery. Its firm and circumscribed character has earned for it the name of potato tumor. The tumor may grow around the artery, so that the vessel becomes embedded in the tumor. It may appear to be malignant, but the tumor does not infiltrate, and operation is inadvisable as the risk is so great. The cells, which are arranged in groups or sheets, are large, granular, and polyhedral, and may contain chromaffin substance (Fig. 243). The tumor is not a chromaffinoma as used to be thought, for the carotid body is not part of the chromaffin system.

**TUMOR OF GLOMUS JUGULARIS.**—Although this tumor arises in the vicinity of the middle ear rather than in the neck, it may be considered here because of its similarity to the carotid body tumor. The glomus jugularis or tympanic gland is a tiny structure analogous to the carotid body which lies along the tympanic branch of the glossopharyngeal nerve in its course either in the superior bulb of the jugular vein or in the bone canals of the middle ear. It resembles a ball of winding capillaries separated by a delicate stroma containing numerous epithelioid cells rich in



FIG. 243.—Carotid body tumor.  
× 275.



cytoplasm. The tumor, which closely resembles the carotid body tumor, consists of these cells in alveolar arrangement with numerous sinusoidal vessels. It shows a strong tendency to recur on removal, but does not set up metastases. There is often a long history of throbbing and buzzing in the ear with slight loss of hearing.

**SECONDARY CARCINOMA.**—Epidermoid carcinoma of the lip, tongue, mouth, larynx, and esophagus may metastasize to the cervical lymph nodes. The transitional-cell type of carcinoma with a small often undiscovered primary growth in the pharynx or nasopharynx and large secondary tumors in the neck has already been described. Finally there may be lymphatic spread of carcinoma from more distant organs. Owing to the fact that the thoracic duct receives efferents from the supraclavicular and lower deep cervical nodes on the left side before it opens into the innominate vein, these nodes are often involved in abdominal and thoracic cancer. Gastric and bronchogenic carcinoma are the most frequent primary tumors responsible, but even the most distant tumors (ovarian, uterine, testicular) may metastasize to the neck by this route. Malignant supraclavicular nodes on the right side suggest cancer of the right lung (right lymphatic duct).

### THE SALIVARY GLANDS

The parotid gland is more liable to disease than the submaxillary and sublingual, so it will be taken as the type.

**ACUTE INFLAMMATION.**—This may be suppurative or non-suppurative. In *suppuration* the infection may be hematogenous as in acute fevers and pyemia. This is rare. Infection from the mouth by way of Stenson's duct is more common. The pus is prevented from reaching the surface by the dense fascia which covers the gland. It may form a retropharyngeal abscess.

The *non-suppurative* form is *mumps*, one of the commonest diseases of childhood. The gland on both sides is acutely inflamed, swollen, painful, and tender. There is little to be seen in the gland apart from a serous exudate. As there is no suppuration or necrosis, healing is by resolution and the gland is uninjured. A similar lesion is produced in monkeys by a filterable virus from the saliva of cases of mumps. Orchitis (inflammation of the testicle) is a common complication in the adult, but here recovery may not be complete and the testicle may undergo atrophy.

**Mixed Tumors.**—This is the condition commonly called parotid gland tumor but, as it may occasionally occur in any of the salivary glands, in the mucous membrane of the mouth, and in the palate, this name is undesirable and misleading. It is a fairly common slowly-growing tumor of early adult and middle life which begins either in the substance or the surface of the salivary gland, and may continue to increase in size for many years, but at any time growth may stop. It is inherently benign, but after the usual operative procedure (enucleation of the tumor) there is recurrence in from 20 to 45 per cent of cases, the tumor then becoming locally destructive and invasive. Total excision of the gland with removal of the capsule gives infinitely better results. Sometimes after growing slowly for many years it may take on rapid growth and invade the surrounding tissue. The lymph nodes are rarely involved unless the tumor has been interfered with. It is usually encapsulated, but may not be.

The *microscopic appearance* is varied and perplexing, for the tumor appears to consist of both ectodermal and mesodermal elements. It is for this reason that it is called a mixed tumor. The following elements are commonly present in one or other part of the tumor, although it is very difficult to find them all combined in a single microscopic field (Fig. 244): (1) masses of epithelial cells often showing a glandular arrangement, (2) mucoid connective tissue with evidence of production of mucin, (3) cartilage, and (4) lymphoid tissue. The cartilage has been the chief stumbling block, as it seemed to be mesodermal in origin, while the epithelium was of ectodermal origin.



FIG. 244.—Mixed tumor of the parotid. Cartilage above, glandular tissue to the right, mucoid tissue to the left.  $\times 160$ .

The *nature of the tumor* has long been a subject for discussion. It is possible that some of the tumors may arise as the result of the accidental sequestration of embryonal cells during the early and complicated development of the face; such tumors would be true "mixed tumors." It appears probable, however, that the great majority are not really mixed tumors, but are benign epithelial growths (adenomas) of the salivary glands in which there is an exaggerated latent potentiality of differentiation. The difficulty presented by the cartilage is removed by the discovery that this material is not true cartilage. The tumor epithelial cells produce mucin, and this constitutes the origin of the mucinous "connective tissue." This myxomatous material, which stains well with muci-carmines, is homogenous like cartilage, and the cells which it contains may lie free in small spaces around which there may be a fibrillar condensation, so that a pseudocartilage may be produced. It is also possible that true cartilage may be formed

from this material. Proliferating cells seem to be capable of inducing changes in adjacent tissues, so that metaplasia of the stroma of these tumors may give rise to true cartilage, bone, fat and lymphoid tissue. In studying these tumors one must separate sharply the neoplastic components which comprise the parenchyma from the metaplastic ones which are derived from the stroma (Morehead and Klein). Simard has reported a sweat gland adenoma of the palm with a structure identical with that of mixed tumor of the parotid. In this case the mucous secretion of the epithelial cells had undergone metaplasia into cartilage.

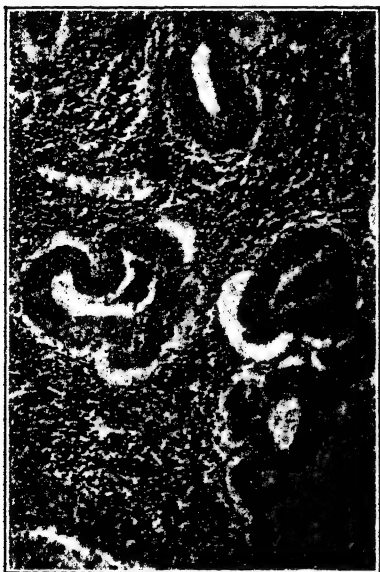


FIG. 245.—Adenolymphoma of parotid gland.  $\times 100$ .

Hellwig points out the resemblance of mixed tumors to the developing notochord, and suggests that these tumors are derived from misplaced elements of that structure. The notochord is in contact with the buccopharyngeal membrane, and on the rupture of that membrane the cells of the two structures may be intermingled. It may be noted that the notochord comes into intimate relation with the developing parotid gland, the submaxillary gland, and the palate, the three common sites of mixed tumors.

**CARCINOMA.**—Carcinoma of the salivary glands grows rapidly, infiltrates the whole gland, involves the regional lymph nodes and sets up distant metastases. It must not be assumed from this brief account that the outcome is necessarily fatal. The tumor may be adenocarcinomatous, medullary, or anaplastic in type.

**ADENOLYMPHOMA.**—This rare tumor of the salivary glands usually occurs in the parotid in the fifth and sixth

decades. It is benign, slowly growing, well encapsulated, and much commoner in males than females. The microscopic picture is characteristic: tubular alveoli lined by tall columnar epithelium supported by an abundant lymphoid stroma with active germ centers (Fig. 245). There may be cystic spaces with papillary projections. The papillary projections may be so pronounced as to justify the high-sounding name of papillary cystadenoma lymphomatosum originally given to the lesion by Warthin. A characteristic feature is the eosinophilic staining of the epithelium which may be very marked. The tumor has been called an *onkocytoma*, because of the suggestion that it may arise from a special type of cell found in the parotid with advancing years characterized by its size (*onkos*, bulk), and known as an onkocyte. These cells are merely acidophilic granular cells which arise from the ducts and acini (Meza-Chávez), so that the term onkocytoma has become meaningless and should be dropped. The association of epithelium, evidently derived from the duct of the gland, and lymphoid follicles is at first sight puzzling. And yet this lymphoepithelial association is not uncommon in tumors of the neck, such as mixed parotid tumor, lymphadenoid goiter, lympho-

epithelioma, branchial cyst, and even normal structures such as the thymus. It would appear that the cells of the part have the potentiality of differentiating in both directions, epithelial and lymphoid (Hicks).

**MIKULICZ'S DISEASE.**—This is a rare benign and chronic condition marked by enlargement of one or more salivary and lachrymal glands. Often only one salivary and no lachrymal glands are involved. As Morgan and Castleman point out the normal parenchyma of the glands is replaced not only by lymphoid tissue but even more characteristically by the intraductal proliferation of cells with the formation of islands in which both epithelial and more peripheral myoepithelial elements can be distinguished. The salivary and lachrymal glands may also be enlarged in the course of leukemia or lymphosarcoma. To this condition the rather misleading name of *Mikulicz's syndrome* has been applied. In such a case, of course, the microscopic picture will be one of lymphoblastoma. The condition may be regarded as a localized form of that disease, but it would perhaps be better to abandon the name.

**UVEO-PAROTID FEVER.**—This is a clinical syndrome characterized by chronic inflammation of the uveal tract (iris, ciliary body, choroid) and both parotids. The parotids are swollen, and the occasional enlargement of both lachrymal glands may lead to a mistaken diagnosis of Mikulicz's disease. Irido-cyclitis and facial paralysis are common. The course is generally febrile, but there is a marked tendency to spontaneous recovery. The condition used to be regarded as a low grade form of tuberculosis, but it is now believed to be a variety of sarcoidosis.

**SALIVARY CALCULI AND CYSTS.**—A *salivary calculus* usually forms in Stenson's duct, and the saliva collects above the obstruction during a meal, causing a cystic swelling of the parotid which gradually subsides after the meal. A *ranula* is a cyst of the sublingual gland, and is therefore situated in the floor of the mouth under the tongue, where it forms a bluish nodule. Occasionally the submaxillary gland is involved.

## THE ESOPHAGUS

The common lesions of the esophagus are carcinoma, stricture, and diverticulum.

**Carcinoma.**—Cancer of the esophagus shows the usual sex incidence of alimentary canal neoplasms, over 80 per cent being in men. Cancer of the hypopharynx (postericoid cancer) is sometimes included with cancer of the upper end of the esophagus; indeed it is often impossible to determine in which region the tumor originated. When this is done the sex incidence of upper end tumors is overwhelmingly female. The commonest site is the middle where the esophagus is crossed and constricted by the left bronchus, followed rather closely by the lower end. The middle, which is the narrowest part, and the lower end are the regions where irritants (food and drink) are delayed longest. The least common site is the upper end, but if cancer of the hypopharynx is included, the incidence practically equals that of the lower end. The tumor begins as a nodule in the mucous membrane, and sometimes grows into the lumen as a bulky mass, but usually takes the form of a diffuse infiltration which slowly encircles the esophagus and causes marked narrowing of the lumen with dilatation of the proximal part of the tube. Ulceration of the surface occurs sooner or later, and the growth may ulcerate into the trachea, into the aorta with fatal hemorrhage, or into the mediastinal tissues with gangrenous inflammation. The stenosis gives rise to marked difficulty in swallowing. The prognosis used to be hopeless,

but modern surgery can remove the diseased esophagus and provide the patient with a new one. The earliest diagnosis can be made with the aid of the esophagoscope. *Microscopically* the tumor is an epidermoid carcinoma, but usually without epithelial pearls or much cornification. Occasionally it may be an adenocarcinoma, which probably arises from anomalous glands in the wall of the esophagus identical with the gastric glands.

*Spread.*—Spread, as is usual in epidermoid carcinoma, is to the regional lymph nodes. These may be mediastinal, cervical, or abdominal. If the cancer is at the upper end of the esophagus, the cervical as well as the mediastinal glands will be involved; a tumor in the middle of the esophagus will spread to the mediastinal glands; with tumors of the lower end, metastases are formed below the diaphragm in the coelic chain of glands and in the liver.

**Stricture.**—Stricture of the esophagus may be organic or functional.

*Organic or cicatricial stricture* is caused by scar formation due to the swallowing of corrosive or boiling fluids, and more rarely to laceration produced by impacted foreign bodies. Fibrous tissue is produced as the result of the injury usually at the upper or lower ends, and this becomes dense scar tissue which encircles the esophagus and causes an extreme degree of stenosis which it may be very difficult to dilate. The esophagus may be narrowed owing to pressure from without by an aneurism of the aorta, a tumor of the lung, or a mass of enlarged lymph nodes.

*Functional or spasmodic stricture or cardiospasm* occurs in young men and women of neurotic temperament. The muscular sphincter at the lower end of the esophagus and the cardiac end of the stomach remains closed and thus prevents food from entering the stomach. The esophagus immediately above the site of the spasm may become dilated and hypertrophied. The distention may become much more extreme than in organic stricture, because there is more time for it to develop, as the patient may live for many years. In middle-aged women and more rarely in men there may be *dysphagia with anemia* (Plummer-Vinson syndrome). Here the cricopharyngeus sphincter between pharynx and esophagus remains closed and fails to open during deglutition. The anemia is probably secondary to the deficient diet. The mucous membrane of the pharynx and tongue is dry and parchment-like. In the roentgen-ray picture the lower end of the esophagus presents a characteristic blunt-pointed appearance, like the end of a cigar, quite different from the appearance in carcinoma. It is probable that both of these forms have a neurogenic basis, a preponderance of sympathetic activity over that of the vagus. In some cases of cardiospasm, inflammatory lesions of Auerbach's plexus have been found at the lower end of the esophagus. It is possible that the condition is rather an inability of the sphincter to relax than an actual spasm, to which the name *achalasia* (*a*, not + *chalis*, relaxation) is applied. This may also be the basis of Hirschsprung's disease, where a persistently closed rectal sphincter leads to great dilatation of the colon in children.

**Diverticula.**—A diverticulum of the esophagus may be of the anterior or posterior variety. The *posterior* variety is much the commoner. It is really a pharyngeal rather than an esophageal diverticulum, occurring in the pharyngeal wall at its junction with the esophagus. It is usually found in men of middle age. The chief cause is probably prolonged intrapharyngeal pressure due to failure of what Chevalier Jackson calls the "cricopharyngeal

pinchcock" to relax during swallowing. The mucous membrane of the lower part of the posterior wall of the pharynx becomes protruded between the oblique and transverse fibers of the cricopharyngeus muscle, so that a sac is formed behind the esophagus which pushes that structure forward. The condition tends to become steadily worse through the accumulation of food in the sac, and pressure on the esophagus may cause difficulty in swallowing. The *anterior* variety occurs at the level of the bifurcation of the trachea, and is due to traction of tuberculous tracheobronchial lymph nodes which have become adherent to the esophagus. The posterior form is thus a pulsion diverticulum, the anterior form a traction diverticulum.

*Varices* may occur at the lower end of the esophagus in cirrhosis of the liver. Rupture of these varicose veins may cause fatal hemorrhage. Varices may occur apart from cirrhosis owing to extensive tumor formation and other lesions of the liver. Sometimes no obvious cause can be found in the liver or elsewhere. These cases must be regarded as idiopathic. *Rupture of the esophagus* may be *traumatic* (due to passage of a bougie or esophagoscope), or spontaneous. *Spontaneous* rupture is a rare condition which occurs after prolonged vomiting and is probably due to acute inflammation of the lower end of the esophagus. The pleural cavity is filled with dirty fluid, and the condition is rapidly fatal. *Digestion* of the esophagus may be *postmortem* or *antemortem*. The former is associated with postmortem digestion of the stomach. *Antemortem digestion* is not uncommon and can be distinguished from postmortem digestion by the presence of an inflammatory reaction in the wall of the esophagus. It occurs in postoperative conditions with marked vomiting, and is probably due to retention of acid vomited material in the lower part of the esophagus. Perhaps a better name is acute ulcerative esophagitis. The lesions are ulcerations and the ulcers vary in type from mere superficial erosions to deep perforating lesions. Only the lower part is involved. It may lead to rupture, and at autopsy the pleural cavity is filled with stomach contents. *Leukoplakia* is not uncommon in the lower part of the esophagus. *Tuberculous* and *syphilitic ulcers* are rare conditions. *Fibromas* and other innocent tumors sometimes occur and form polypi. *Sarcoma* is very rare.

## ADDITIONAL READING

- Acute Ulcerative Esophagitis.** BARTELS: Arch. Path., 1935, 20, 369.  
**Adenolymphoma of Salivary Glands.** CARMICHAEL, *et al.*: J. Path. and Bact., 1935, 40, 601. HARRIS: Am. J. Path., 1937, 13, 81. HICKS: J. Path. and Bact., 1953, 65, 169. MARTIN AND EHRLICH: Surg., Gynec. and Obst., 1944, 79, 611. MEZA-CHÁVEZ: Am. J. Path., 1949, 25, 523.  
**Branchial Cleft Carcinoma.** OLIVER: Am. J. Cancer, 1935, 23, 16.  
**Cancer of the Mouth.** MARTIN AND KOOP: Am. J. Surg., 1942, 57, 195.  
**Carotid Body Tumor.** GRATIOT: Internat. Abstr. Surg., 77, 177; in Surg., Gynec. and Obst., 1943. LECOMPTE: Am. J. Path., 1948, 24, 305.  
**Intra-oral Tumors.** CUTTER: Arch. Surg., 1929, 18, 2303.  
**Mikulicz's Disease.** LEUCUTIA AND PRICE: Am. J. Roent., 1930, 24, 491. MORGAN and CASTLEMAN: Am. J. Path., 1953, 29, 471.  
**Nasopharyngeal Tumors.** GARDHAM: Brit. J. Surg., 1929, 17, 242.  
**Salivary Gland Tumors.** HELLWIG: Arch. Path., 1945, 40, 1. HOUCK: Surgery, 1939, 6, 550, 565. McFARLAND: Am. J. Med. Sci., 1942, 203, 502. MOREHEAD AND KLEIN: Am. J. Path., 1953, 29. PATEY: Brit. J. Surg., 1930, 18, 241. RAWSON, *et al.*: Cancer, 1950, 3, 445. SHELDON: Arch. Path., 1943, 35, 1. SIMARD: Am. J. Cancer, 1938, 33, 182.  
**Tuberculosis of Tongue.** FINNEY AND FINNEY: Surg., Gynec. and Obst., 1925, 14, 743.

## Chapter

## 19

# THE STOMACH AND DUODENUM

### GASTRITIS

INFLAMMATION of the stomach, either acute or chronic, is due to the action of irritants. But the irritant does not necessarily act on the surface. The most important part of the gastric mucous membrane is not the surface epithelium but the deep portion containing the gastric glands, and this deep portion is more likely to be reached by an irritant carried by the blood stream than by mere surface irritation. The causes of gastritis are not very certain, but they may be divided into: (1) surface irritants such as alcohol, irritating foods, and corrosive poisons, and (2) blood-borne irritants, *e. g.*, bacteria.

**Acute Gastritis.**—Surface irritants may readily cause an acute gastritis, which must be present to some extent after every severe alcoholic bout, and is largely responsible for the “morning after” feeling. It may also occur in the acute fevers. The mucosa is reddened and shows as a rule merely catarrhal changes. It is difficult or impossible to separate these from the postmortem changes which invariably occur as the result of digestion unless formalin be injected into the abdominal cavity immediately after death, in which case the gastric mucosa is as fresh and well fixed as if it had been removed at operation. The action of *poisons* on the stomach has already been considered in Chapter 13. It may be repeated here that carbolie acid coagulates and fixes the mucosa perfectly, the corrosive acids produce destruction and often perforation, and the caustic alkalis cause necrosis with marked softening so that here also perforation may occur. *Membranous gastritis* and *phlegmonous gastritis* are rare conditions in which there is extensive invasion of the stomach wall by bacteria, often streptococci, with violent inflammation and necrosis over a wide area and to a great depth.

**CHRONIC GASTRITIS.**—The causes of chronic gastritis are not well understood. Alcohol is always incriminated, but in gastroscopic examinations made by Gray and Schindler on 100 alcoholic addicts who had consumed an average of 2.8 pints of alcohol daily for more than twenty years, the stomach was essentially normal in 55 per cent, nor was any correlation observed between the incidence or severity of the gastritis and the duration of the alcoholism or the amount of alcohol consumed. Almost identical findings are reported by Berry. The disease takes two forms, hypertrophic and atrophic. *Hypertrophic gastritis* is the commoner of the two. There is marked thickening of the mucosa, especially in the pyloric region. The surface becomes divided into little areas so as to have a finely nodular appearance, a condition known as *état mammelonné*. The polypoid formation known as *gastritis polyposa* is neoplastic rather than inflammatory and will be considered in con-

nection with tumors. *Microscopically* the glands of the mucosa are separated by a diffuse infiltration of lymphocytes, plasma cells, and eosinophils, with a varying degree of fibrosis in the submucous coat. The glands suffer and atrophy, some become cystic, but most of them disappear, so that the mucosa is a mass of granulation tissue covered by epithelium rather than a parenchymatous structure. Such a mucous membrane cannot be expected to secrete hydrochloric acid, so that achylia gastrica develops.

*Atrophic gastritis* may probably be a sequel to the hypertrophic form or may develop independently. It is often associated with constitutional disturbances, especially pernicious anemia. The mucosa is markedly thinned, the glands atrophic and widely separated, the muscle fibers attenuated, and all the coats more or less fibrosed. An intestinal type of epithelium may replace much of the gastric mucosa. As the secreting membrane is so atrophic, achylia gastrica is always marked.

EFFECTS OF GASTRITIS.—Chronic gastritis in the pyloric region may give rise to the classical symptoms of gastric ulcer, *i. e.*, hunger pains, hypersecretion, and delayed emptying and stasis, but when gastrectomy is done no ulcer is found. European investigators find that gastric ulcer and chronic gastritis are frequently associated, and believe that the gastritis precedes the ulcer. In surgical material it is certainly the case that some degree of gastritis is almost always present in gastric and duodenal ulcer. When the gastritis is at all diffuse there is likely to be *achylia gastrica*. This is a very common consequence of chronic alcoholism, especially in elderly persons. Achylia may be due to hematogenous infection in the infective fevers such as influenza and typhoid, and may persist for years afterward. It occurs in over 30 per cent of cases of pulmonary tuberculosis, and in many cases of the toxemia of pregnancy. Complete achylia is always present in pernicious anemia and usually in cancer of the stomach.

## PEPTIC ULCER

The stomach and the first part of the duodenum are both derived from the foregut, are both supplied with blood from the coeliac axis, and are both bathed by acid gastric juice, as the alkaline bile and pancreatic secretion flow into the second part of the duodenum. Ulcer of the duodenum is for practical purposes ulcer of the first part, and as gastric and duodenal ulcers are essentially the same in their pathology and are dependent for their production on the peptic juice, they may be considered together under the heading of peptic ulcer. Peptic ulcers also occur on the jejunal side of a gastro-enterostomy and in Meckel's diverticulum.

ETIOLOGY.—The cause of peptic ulcer has long been a matter of debate, nor has any agreement yet been reached. The views may be summarized by saying (1) that the digestive power of the gastric juice may be so increased that it corrodes the normal healthy mucosa, or (2) that the damaged mucosa cannot resist the action of the normal hydrochloric acid and pepsin. It can be said here that high acidity for long periods, especially at night when the stomach has emptied its contents into the duodenum, may possibly explain duodenal but not gastric ulcer. A biopsy taken through the gastroscope heals as quickly when the acidity is high and continuous as in cases of achlorhydria. The ulcer is produced by the action of the



gastric juice, but no one has explained how it is that the stomach does not digest itself. Living healthy tissue evidently resists digestion, for when kidney or spleen with circulation intact are introduced into the stomach they are not digested, even when the cut surface is exposed to the gastric juice for weeks or months. A peptic ulcer, and in particular a chronic ulcer, is the result of the continued action of the gastric juice on an area of mucous membrane which is presumably of lowered resistance. The real difficulty is to decide the cause of the lowered resistance. There are three principal views: the infective, the chemical and the neurogenic.

A plausible and popular theory is that *hematogenous infection* with organisms of low grade virulence may cause inflammatory foci in the stomach wall leading to necrosis with subsequent digestion and ulcer formation. In a large series of cases Hebbel found that an atrophic gastritis (gastritis leading to atrophy) affecting the antrum was an invariable accompaniment of gastric and duodenal ulcer. It seems reasonable to suppose that the gastritis precedes and is the anatomical basis for the development of ulcer, and that chronic ulcer does not develop in a healthy mucosa. Gastritis is not nearly so frequent an accompaniment of gastric carcinoma, nor is it confined to the antrum.

Cushing revived the *neurogenic theory* that abnormal vagal impulses from the hypothalamic region of the diencephalon are responsible for vascular spasm and ischemia which cause the initial area of necrosis. Ulcer may complicate tumors and inflammation of this region. It is undoubtedly more common in the nervous high strung patient, in whom worry and strain may precipitate an attack. The neurogenic factor is the most important single etiologic agent in many cases of ulcer. Indeed the experimental and clinical observations of Dragstedt suggests an intimate connection between the neurogenic and chemical theories, for the hypersecretion of gastric juice in ulcer patients appears to be due to a continuous hypertonus of the gastric secretory fibers in the vagus nerves. The paramount importance of this factor is emphasized by the spectacular therapeutic results which may follow bilateral division of the vagus nerves (vagotomy), the gastric secretion being greatly reduced and the ulcers tending to heal. It may be noted that vascular density of the mucosa is lower in the ulcer area than elsewhere in the stomach, as shown by microradiographs of material injected with a contrast medium (Doran).

According to the *chemical theory* the essential factor is the action of excess acid. Hyperacidity is a constant accompaniment of peptic ulcer in the early stages, although it may disappear in old chronic ulcers. The fact that the ulcer occurs in non-acid-producing mucosa although in immediate juxtaposition to acid-producing mucosa must be significant. Of even greater significance is the fact that peptic ulcer occurs in a Meckel's diverticulum containing acid-producing gastric mucosa. Food, which is the normal stimulus for the formation of gastric juice, is the chief agent which protects the tissues against its corrosive activities. Also protecting the stomach and duodenum are the pancreatic juice, gastric mucus, duodenal juice and bile. It is important to remember that the gastric juice is secreted continuously, even during prolonged fasting. It is during the night when the protective factors are absent that the worst

damage may be expected. This damage may be better visualized when it is recalled that between 2,000 and 3,000 cc. of gastric juice are secreted in the space of twenty-four hours. The night secretion is reduced by vagotomy to the extent of 50 per cent. Worry and nervous strain are associated with hyperacidity, perhaps explaining the prevalence of ulcer amongst surgeons. It has already been pointed out that the ulcer patient is frequently nervous and high strung. Food which causes hypersecretion may lead to the formation of ulcer. Thus in Abyssinia, where peptic ulcer is extraordinarily common, a favorite and universal sauce contains 50 per cent cayenne pepper (Bergsma). The experimental injection of histamine, which stimulates gastric acidity, results in the production of ulcers, especially when the histamine is implanted in beeswax to prolong its action. In severe burns histaminoid substances are produced, and it has long been known that such burns may be accompanied by the formation of acute ulcers in the stomach and particularly in the first part of the duodenum, a condition known as *Curling's ulcer*. This type of ulcer is found in 12 per cent of dogs in which large burns were produced. The subcutaneous injection of posterior pituitary extract produces acute hemorrhagic lesions, whilst repeated injections produce chronic ulcers of the peptic ulcer type (Dodds). If the stomach contents are rendered alkaline, injection of pituitary extract fails to produce ulcers. The most effective method of inducing an ulcer to heal, provided it is not too chronic, is by neutralizing the gastric acidity, especially by means of the continuous drip method. All of these facts point to the paramount importance of gastric acidity in the production and maintenance of peptic ulcer, although they do not prove that some additional factor may not also be operative.

That food deficiency may play a part in some regions is suggested by the extreme frequency of duodenal ulcer in Southern India, particularly Travancore (Somervell). In this district food consists of rice and curry, poor in all the vitamins, particularly A and B<sub>2</sub>. In some parts of India, such as the Punjab, where the diet is rich and well-balanced, peptic ulcer is singularly rare.

In spite of all the theories peptic ulcer still remains a mystery. We cannot explain the site, nor the sex incidence, nor why there has been an apparent shift from the stomach to the duodenum, from women to men, and from youth to middle age.

**SYMPTOMS.**—The chief symptom of peptic ulcer is pain which is relieved by the taking of food. In duodenal ulcer the sequence is food—comfort—pain, whereas in gastric ulcer it is usually food—comfort—pain—comfort. The sequence may be repeated for weeks or months; then there may be a period of freedom, only to be followed by another attack. Hemorrhage, perforation, and obstruction due to pyloric stenosis are important complications.

**LESIONS.**—It is not easy to determine the true *relative frequency* of chronic gastric ulcer as compared with duodenal ulcer. Surgical statistics show that chronic ulcer is much commoner in the duodenum. In the Toronto General Hospital out of 875 cases of chronic ulcer coming to operation 70 per cent were in the duodenum and 30 per cent in the stomach. It must be remembered, however, that the surgeon sees a special class of cases, those in which symptoms of obstruction form a prominent feature.

In the autopsy material of the same hospital gastric ulcers were nearly twice as common as duodenal. On the other hand Hurst and Stewart found duodenal ulcers somewhat more frequent in their autopsy material.

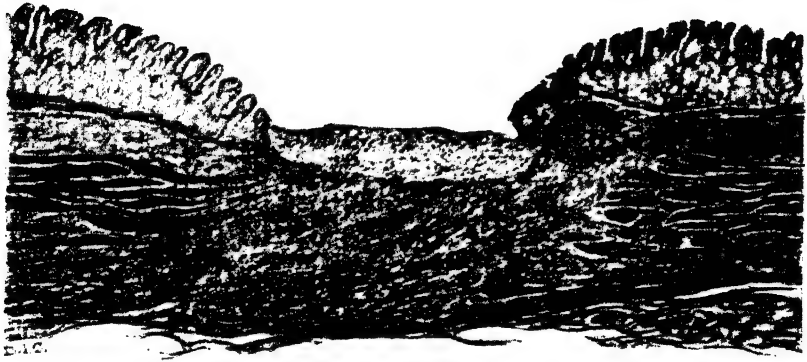
The *sex incidence* of peptic ulcer has shown a notable change during the past half century. In the earlier part of this period Alsted found that in Denmark the incidence of males to females was 1 to 5; by the beginning of the century it was 1 to 1; in the decade from 1920 to 1930 it had risen to 3 to 1. This is due to the increased frequency of duodenal ulcer, which is commoner in the male. *Acute* ulcers may occur in any part of the stomach. They are usually shallow, more of the nature of erosions, but occasionally they may perforate the whole thickness of the wall. The *chronic* peptic ulcer is much more localized. Duodenal ulcers are practically always limited to the first part of the duodenum, usually on the anterior wall so that perforation is relatively common, as the ulcer in this position cannot become adherent to the abdominal wall. The vast majority of ulcers occur along the line of the lesser curvature or in close proximity to it. It is rare in the region of the cardia, in the fundus and on the greater curvature, and is uncommon in the pyloric canal (about 1 inch in length). The site of election is between 2 and 4 inches from the pylorus, whereas cancer is commonest in the juxtapyloric portion. Sometimes the ulcer is placed astride the lesser curvature (*saddle-shaped ulcer*). When such an ulcer heals the stomach will be divided into two parts, a condition known as *hour-glass stomach*. The fundus glands produce acid, whereas the glands in the pyloric (large) and cardiac (small) zones do not. The line between the acid and non-acid-producing areas is known as the acid line. The zone of pyloric glands, and therefore the *acid line*, reaches much higher on the lesser than on the greater curvature. The line varies considerably in position in different stomachs, and can readily be determined by opening the stomach along the greater curvature and taking blocks of tissue along the lesser curvature.

Peptic ulcers do not arise in the area of acid production. They are formed immediately on the pyloric side of the varying acid line. It is of particular interest to note that peptic ulcers in Meckel's diverticulum are situated in the intestinal type of mucosa, not the heterotopic acid-producing mucosa.

The *gastric ulcer* is usually single but may be multiple (5 to 10 per cent). It is shaped like a funnel, penetrating the muscular coat sometimes as far as the peritoneal surface (Fig. 246). Small ulcers tend to be circular and larger ones oval. The sides are generally sloping but may be steep; the cardiac side of the ulcer is steeper than the pyloric. The edge is raised, often overhanging, and the floor is hard and indurated. The larger the ulcer, the more likely is it to be malignant. Most simple ulcers are less than 1 inch in diameter, but some may attain a much larger size. On the peritoneal surface the presence of the ulcer is indicated by pallor and well-marked induration so that it can be felt better than seen.

A *duodenal ulcer* situated in the first part of the duodenum, or more specifically the duodenal bulb (pyloric cap), is usually small and associated with marked cicatricial contraction, so that small diverticula are often

## PLATE XI



### Chronic Peptic Ulcer

Both the muscularis mucosæ and the muscular coat are replaced by scar tissue. (Aniline blue connective-tissue stain.)

formed between the ulcer and the pylorus. In very chronic and especially in healed ulcers cicatricial contraction may shorten the distance between the pylorus and the papilla from the normal 8 to 6.5 cm. or less.

*Microscopically* in well-fixed surgical material four zones can be distinguished in the floor of the ulcer (Fig. 247): (1) an inflammatory zone consisting of fibrin and polymorphonuclear leucocytes; (2) a zone of necrotic granulation tissue; (3) a zone of living granulation tissue; (4) a zone of dense scar tissue which forms one of the most important features of the ulcer. (Plate XI.) It extends in the submucosa for some distance under the intact mucous membrane, and materially interferes with healing in preventing the approximation of the edges (Fig. 248). When a chronic



FIG. 246.—Peptic ulcer. This is a characteristic example of an innocent ulcer of the stomach.

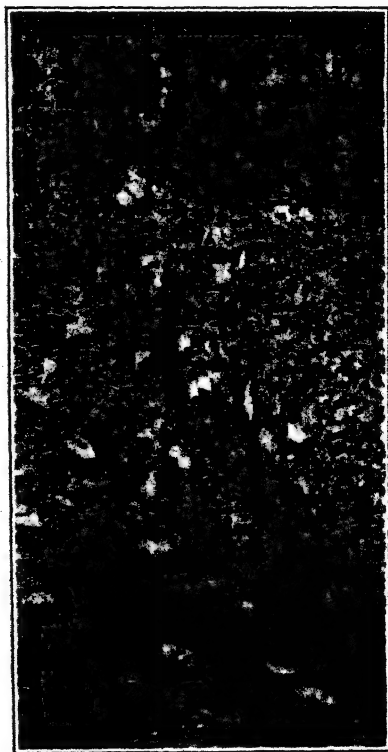


FIG. 247.—Peptic ulcer showing zones of necrosis, granulation tissue, and fibrosis.  $\times 200$ .

peptic ulcer reaches a certain stage it simply cannot heal. There is nearly always greater destruction of the muscular coat than of the mucosa. Evidence of active inflammation in the shape of dilated vessels and foci of chronic inflammatory cells can be seen even in the most quiescent scar tissue, showing that irritation is still going on. The vessels are often narrowed by very marked endarteritis obliterans. At the *margin* of the ulcer there may be evidence of epithelial proliferation in the form of down-growths, and glandular tissue may be found beneath the muscularis mucosae.

These changes are apt to be wrongly interpreted as indicating carcinoma.

**HEALING.**—Acute ulcers and erosions heal rapidly and easily. Chronic ulcers may also heal though with difficulty. It appears likely that an ulcer may heal, recur, break down, and heal again, with each recurrence becoming deeper and more fibrotic. Healing is interfered with by (1) the acid gastric juice, (2) the necrotic layer on the base which covers the granulation tissue and provides no footing for the ingrowing epithelium, and (3) the dense scar tissue which prevents approximation of the edges. *Microscopically* the leucocytes and necrotic tissue disappear, the ulcer becomes



FIG. 248.—Peptic ulcer. The submucosa is extensively fibrosed. There are large collections of inflammatory cells far below the surface of the ulcer.

filled with healthy granulation tissue, over which the mucosa grows as a single layer of flat cells which later become typically columnar and form tubular glands. The young mucosal cells are at first very fragile and easily destroyed by the passage of gastric contents over the ulcer.

**The Relation of Symptoms to Lesions.**—The great symptom is *pain*, relieved by the taking of food and alkalis. It is when the stomach is empty that the pain is most severe, so that the patient may have to get up in the middle of the night to eat a biscuit or drink a glass of milk. There are two possible explanations of the pain, both of which have warm supporters. (1) It may be due to the acid gastric juice acting on the raw surface of the ulcer. As the acidity is neutralized by food or alkalis the pain becomes relieved. When the ulcer becomes perforating the pain is no longer relieved by alkalis. (2) The pain may be muscular in nature and unconnected with the action of the acid juice on the ulcer. The inflammatory foci in the muscularis give rise to contractions in the neighborhood of the ulcer and especially at the pylorus. These increase the intragastric pressure and the tension of the muscle fibers, and this increase is reflected in the sensation of pain.

A patient may present a typical history of peptic ulcer, yet operation may reveal no lesion in the stomach or duodenum. These organs receive the same double nerve supply (sympathetic and parasympathetic) as the other abdominal organs, and the possibility of reflected painful sensations must be borne in mind. The stomach is like a sensitive receiving set which tunes in to distant stations; at the same time it is an amplifier and loud speaker which magnifies any notes of distress it may receive. Not only may all the symptoms of ulcer be present without an ulcer, but a well-developed ulcer may be present without symptoms. These facts do not make the task of explaining the clinical picture any easier.

The other symptoms are rather in the nature of complications. *Hemorrhage* is very common. It is due to erosion of a vessel in the floor of the ulcer. If the hemorrhage is severe the blood will be vomited; when the blood has been retained in the stomach and altered by digestion the vomitus will have a brown (coffee-ground) appearance. If the hemorrhage is slight it may only be detected in the form of occult blood in the stools. Minute erosions may cause oozing of blood from the mucosa (gastrostaxis). *Perforation* is more likely to occur in ulcers with a very short history in which there is rapid penetration of the muscular wall. In ulcers of long standing there are likely to be adhesions between the ulcer on the posterior wall of the stomach and such organs as the liver and pancreas. The long-continued administration of cortisone has increased the danger of perforation. As duodenal ulcer is commoner on the anterior than the posterior wall, perforation is more likely to occur in this form of peptic ulcer. *Cicatricial contraction* at the pylorus will cause pyloric stenosis and great dilatation of the stomach. If the ulcer is on the lesser curvature the scar tissue may pull upon the greater curvature causing the constriction characteristic of hour-glass stomach.

**MALIGNANT CHANGE IN GASTRIC ULCER.**—On this important question much difference of opinion exists. The matter is important because the outlook on treatment (medical or surgical) is so much influenced by the answer to the question. There is no doubt that a chronic peptic ulcer *may* become carcinomatous, just as an ulcer in any part of the body may undergo malignant change. The important question is, *how often* does this occur? The difference of opinion depends largely on different interpretations of the microscopic appearance. To one pathologist the presence of isolated abnormal epithelial cells and aberrant tubules in the neighborhood of a tumor spells carcinoma, while to another they are the result of distortion produced by the contracting fibrous tissue or merely part of the regenerative process. In examining a malignant ulcer the following points would be in favor of it representing a malignant change in a peptic ulcer: (1) the edge is carcinomatous but not the base, for the latter is densely fibrous and resists invasion by carcinoma cells; (2) marked endarteritis; (3) complete destruction of the muscular coat and its replacement by fibrous tissue; (4) fusion of the muscularis mucosæ and the muscular coat at the margin of the ulcer due to healing.

The site of election of the lesion suggests that malignant change is not of common occurrence. The majority of cancers are situated at the pylorus, whereas the majority of ulcers are from 2 to 4 inches from the pylorus.

The *clinical evidence* is as important as the pathological. The true ulcer cases have a history of many years' duration, whereas in cancer there is usually a history of only a few months' gastric disturbance, the patient often remarking that previously he was "able to digest nails." If cancer

were often preceded by ulcer the reverse would be the case. Finally, ulcer of the duodenum is very common and cancer of the duodenum is extremely rare. Occasionally the symptoms of ulcer may change into those of cancer, the pain becoming continuous and losing its relation to food. The most reasonable figures appear to be as follows: about 5 per cent of chronic gastric ulcers become malignant, while about 20 per cent of gastric cancers arise from a preëxisting ulcer.

**SECONDARY JEJUNAL ULCER.**—After the operation of gastro-enterostomy for peptic ulcer a secondary ulcer may develop at the gastro-jejunal junction or in the efferent loop of the jejunum within a few inches of the opening (stoma ulcer). This has all the characters of a peptic ulcer. It is caused by the unaccustomed action of the acid gastric juice on the mucosa of the jejunum, together with some accessory factor such as local injury of the mucosa due to the presence of an unabsorbable suture.

### TUMORS OF THE STOMACH

**Cancer of the Stomach.**—Carcinoma of the stomach is the commonest form of malignant disease affecting the internal organs. In Great Britain it is nearly three times as common as cancer of the uterus and twice as common as cancer of the breast. Moreover, on account of its remarkable silence the cure-rate is the worst in malignant disease. About one-half of human cancers occur in the alimentary canal. Such cancers are very rare in all other series of animals. Thus in 142,000 mice only 15 had cancer of the stomach at autopsy (Wells). In the past it has not been possible to produce this very common form in the experimental animal, but squamous cell carcinoma of the forestomach of mice has now been caused by the administration of carcinogenic hydrocarbons dissolved in olive oil (Stewart and Lorenz). The disease is much more frequent in the poorer classes than among the well-to-do. Thus in England it is three times commoner amongst the poor. The geographic incidence is also of interest. In Britain the incidence is 22 per cent of all cancers in men, in America 42 per cent, in Holland 55 per cent, in Czechoslovakia 66 per cent. These differences are probably due to different habits in eating, drinking and chewing tobacco, possibly also to dental hygiene. All of these may lead to chronic gastritis, which is probably a precancerous condition of importance. It may be noted that the incidence is high among stokers and barmen, but low among clergymen. Perhaps the most remarkable fact in the geographic pathology of gastric carcinoma is the almost complete absence of the disease amongst the Malays of Java and Sumatra, whereas primary cancer of the liver heads the list of malignant disease amongst these people (Bonne). Gastric ulcer is equally rare. On the other hand amongst the Chinese of these islands both gastric cancer and gastric ulcer are common, although surpassed in this respect by cancer of the liver. Pernicious anemia seems to be a predisposing cause, now that patients no longer die of that disease. The usual age period is about sixty, but it may occur much earlier. The common site is the pyloric region. About 60 per cent occur in this position, 20 per cent along the lesser curvature and at the cardiac end, while most of the remaining 20 per cent are along the greater curvature. This distribution should be compared with that of peptic ulcer. The question of the relation of



of carcinoma to simple ulcer has already been discussed. About 5 per cent of chronic gastric ulcers may develop into carcinoma.

**SYMPTOMS.**—The chief symptoms are dyspepsia in a man in the cancer age period who has previously had a good digestion, loss of appetite, with pain as a late manifestation. The gastric contents show absence of free hydrochloric, presence of lactic acid and blood. Loss of weight and marked anemia are among the general symptoms.

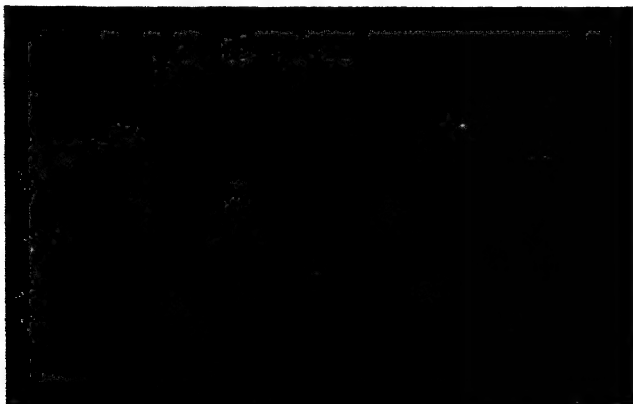


FIG. 249.—Polypoid form of carcinoma of stomach. (Boyd's Surgical Pathology.)

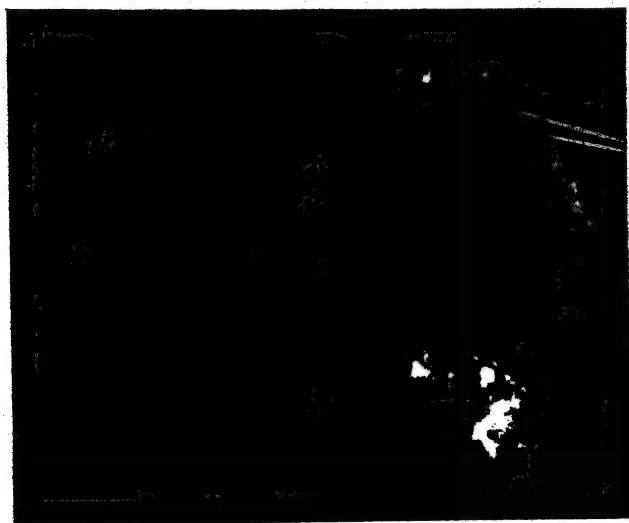


FIG. 250.—Excavating carcinoma of stomach. (Boyd's Surgical Pathology.)

**LESIONS.**—The *gross appearance* varies greatly. (1) The tumor may form a large, soft, fungating mass which projects into the lumen of the stomach like a mushroom. Ulceration of the surface gives rise to infection and hemorrhage. This may be called the *papillary form* (Fig. 249). (2)

More often the tumor is only slightly elevated and early becomes ulcerated. The edges of the ulcer are raised and rounded, and its diameter may be much greater (above 2.5 cm.) than that of the usual peptic ulcer, although there are exceptions to this rule. This variety is the *excavating form* (Fig. 250). A simple ulcer which becomes malignant belongs to this group. The cut surface shows marked thickening of the wall with yellow flecks of necrosis, and sometimes nodules on the serous surface. (3) The *diffuse infiltrating form*, in which no real tumor is seen but a great thickening of the stomach wall. This may be local or diffuse. The *local* form occurs at the pylorus, where there is a dense ring of sclerotic tissue which causes great pyloric stenosis and marked dilatation of the stomach (Fig. 251).



FIG. 251.—Carcinoma of the stomach. This is an example of the local pyloric form the infiltrating variety.

The cut surface is greatly thickened and densely hard. The *diffuse* variety is known as *linitis plastica*, cirrhosis of the stomach, and leather-bottle stomach. The entire stomach is involved; it is very small and very thick walled. The normal stomach is about 12 inches long and contains 40 ounces; the leather-bottle stomach may only measure 4 inches and contain only 4 ounces. The wall may be an inch thick. The walls of the stomach are peculiarly stiff and rigid. There is no ulceration of the surface, but the mucosa is firmly tacked down to the underlying muscular coat. The stomach is involved from the cardia to the fundus; the thickening stops abruptly at the pyloric ring and does not invade the duodenum. On the other hand it may invade far into the esophagus. In the diffuse form it may be very difficult to demonstrate any cancer cells, most of which seem to die out, so that the condition is of low malignancy.

The *microscopic appearance* varies considerably. Although the stomach is a glandular organ, cancer frequently fails to form even rudimentary

glands. The cells are usually arranged in cords or masses, or seen as isolated cells. This is in marked contrast to cancer of the bowel, in which an adenomatous arrangement is nearly always well marked. The polypoid (less malignant) form is likely to show the best examples of glandular arrangement (Fig. 252). The normal mucosa is replaced by atypical glandular tubules which penetrate the muscularis mucosæ, spread widely in the submucous coat, and may finally appear on the serous surface. The glands are lined by one or several layers of cells with large hyperchromatic nuclei so that the tubules appear much darker than the surrounding normal ones. In other cases the tumor is more anaplastic, glandular acini are poorly formed or completely absent, and the cancer cells are arranged in



FIG. 252.—Carcinoma of stomach. The rudimentary glands to the left are highly malignant in type.  $\times 300$ .

masses or in single columns separated by a dense stroma of the scirrhous type. Such a picture is more likely to be seen in ulcerocarcinoma. The most extreme anaplasia is met with in the diffuse infiltrating variety, but in spite of the anaplasia the tumor is not of a high grade of malignancy. Here there is no attempt at gland formation, and the individual cells or clumps of cells are lost in a scar-like stroma so dense that it appears to be strangling them. Many of the cancer cells contain droplets of mucin which can best be demonstrated with the periodic acid-Schiff stain, a valuable method of identifying malignant cells embedded in dense fibrous tissue. When the mucin production is excessive the tumor is converted into a soft gelatinous mass; this variety is called *mucoid carcinoma*, formerly known as colloid cancer, and forms about 5 per cent of gastric carcinomas. The cells are distended and finally destroyed by clear mucinous material, but

clumps of recognizable carcinoma cells are found here and there. The change does not affect the prognosis.

*Gastritis and Carcinoma.*—The mucous membrane not only in the immediate neighborhood of the tumor but also at a distance may show chronic gastritis, either atrophic or hyperplastic, with atrophy of the peptic cells and tubules, and a transformation of the gastric into the intestinal type of cells with many goblet cells. The changes are associated with an early diminution or disappearance of the hydrochloric acid in the gastric juice. The gastritis, which is much more evident in surgical than in autopsy material, may be regarded as a precancerous condition, and by some these changes are believed invariably to precede carcinoma. In other words, carcinoma does not originate in a normal stomach.

*Spread.*—Cancer of the stomach spreads locally, to the lymph nodes, and to distant organs. (1) *Local spread* occurs both in the stomach wall and to neighboring organs. Spread in the stomach wall takes place mainly in the loose submucous coat. In the diffuse infiltrating form the entire submucosa is first infiltrated and then becomes fibrosed. The tumor may penetrate the entire thickness of the wall and appear on the serous surface, from which the tumor cells may be spread by implantation over the abdomen (peritoneum, omentum, ovaries). The duodenum is never invaded, the tumor stopping short at the pylorus. Spread to neighboring organs usually involves the liver or the pancreas when the cancer is on the posterior wall of the stomach. (2) *Spread to the lymph nodes* is extremely common. At first the regional nodes draining the stomach are affected, but there may be distant spread along the thoracic duct, and the supraclavicular and cervical glands may be enlarged, especially on the left side. (3) *Spread to distant organs* is by the blood stream. The liver is involved first and most frequently *via* the portal vein. It may be enormously enlarged though the gastric tumor may be too small to be detected clinically. There may be blood spread to the lungs, central nervous system, kidneys and bones. The abdominal organs, especially the ovaries, may be the site of metastases, either by implantation or by lymphatic spread.

*THE RELATION OF SYMPTOMS TO LESIONS.*—*Pain* as an early symptom is unfortunately absent in about one-half the cases of cancer of the stomach, for it depends on destruction and irritation of the muscular coat; quiet infiltration by tumor cells may cause little irritation. Pain is likely to be present in ulcerocarcinoma, and when the tumor is at the pylorus where it excites spasm. If the pain of chronic peptic ulcer in a man in the cancer age changes its character, becomes continuous, and loses its relation to food, a malignant change is probably taking place. *Loss of appetite* and a sense of satiety before the meal is finished are due to the carcinomatous infiltration of the muscular coat interfering with the healthy tonus upon which the sensation of hunger depends (Fig. 253). *Absence of free hydrochloric acid* in the stomach contents is due partly to the destruction of the mucous membrane by the tumor, partly to secondary changes which develop in the rest of the mucosa leading to atrophy of the oxyntic cells. The suppression of hydrochloric acid is not so constant or complete as in pernicious anemia. In early carcinoma free hydrochloric acid is often present, and it can be demonstrated by the fractional method in about one-half the operable cases. *Lactic acid* appears as the result of pyloric obstruction and the decomposition of retained food. *Blood* in the stool (occult blood) is a most important and constant sign; it is due to ulceration and will therefore be absent in the diffuse infiltrating form. It can also be found in the stomach contents. *Ex-*

*foliative cytology* has been disappointing owing to peptic digestion of the cancer cells. Mechanical irritation, as by means of an inflatable abrasive balloon, seems to give better results. *Anemia* is very common. It is usually of the secondary type, but is occasionally indistinguishable from pernicious anemia except that the bilirubin in the blood is not above normal. The anemia may be due partly to continued loss of blood, partly to ulceration and sepsis, but the more primary form may well be due to that loss of the power of the stomach to produce the hematopoietic principle (stored later in the liver) which is responsible for pernicious anemia.

**CANCER OF THE DUODENUM.**—Although simple ulcer is so common, carcinoma is rare in the duodenum, but in my experience not so rare as is commonly stated. The usual site is the second part, not the first part as in ulcer. The tumor causes obstruction of the biliary and pancreatic ducts. It is easy to mistake cancer of the head of the pancreas for cancer of the second part of the duodenum.

**SARCOMA.**—This is a rare tumor which forms a large polypoid mass that projects into the stomach. It usually arises from the muscle, so that it is a myosarcoma made up of elongated cells. In lymphosarcoma and Hodgkin's disease there may be local lesions in the gastric mucosa.

**INNOCENT TUMORS.**—These also are rare. The commonest is a *myoma* arising from the muscle fibers and forming a mass in the cavity of the stomach like a submucous fibroid of the uterus. Fibroma, lipoma and hemangioma have been described. *Multiple adenomata* or *diffuse gastric polyposis* is a condition in which soft polypoid masses are scattered over the surface of the mucous membrane or are arranged in a group. The microscopic structure shows an adenomatous formation of new glands. Occasionally one of the adenomata may become malignant. Severe anemia and achylia gastrica are common symptoms.

**ADENOMYOMA** is a rare and peculiar lesion which is confined to the pyloric end of the stomach, but may also occur in the duodenum and jejunum. Forming a localized yellowish nodule in the wall of the stomach (where it may be mistaken for carcinoma) or bowel, it really appears to be a benign neoplasm arising from heterotopic epithelium. It consists of a mixture of pyloric or duodenal (Brunner's) glands and pancreatic tissue arranged in nodules which are surrounded by plain muscle. The lesion is of clinical significance, as it may cause gastric symptoms.

**TUBERCULOSIS.**—This is rare, and is secondary to tuberculosis elsewhere, usually in the lung. The usual lesion is an ulcer, single or multiple, with undermined edges. There may be a lump instead of an ulcer, and sometimes merely a scar. Microscopic examination may reveal tuberculosis in a lesion which has been mistaken for a peptic ulcer or cancer.



FIG. 253.—Carcinomatous invasion of the muscular wall of the stomach. It is this infiltration which destroys the muscle tone and is responsible for the loss of appetite.  $\times 175$ .

## POSTMORTEM DIGESTION

No organ shows postmortem change so quickly as the stomach, because after death the anti-enzymes disappear which prevent the gastric juice from acting on

the stomach wall during life. There may be mere softening of the mucosa at the cardiac end so that it can be scraped off, or the gastric juice may eat a hole in the stomach wall at the cardiac end and sometimes in the diaphragm, so that gastric contents are found in the abdominal and pleural cavities. To distinguish this from an antemortem condition (which may be of importance in suspected foul play), the edges of the opening are examined microscopically for evidence of reaction, which of course is absent if the lesion is a postmortem one.

### CONGENITAL PYLORIC STENOSIS

This is a condition of congenital hypertrophy of the pylorus usually occurring in male breast-fed infants. The pylorus is greatly thickened so that it projects into the duodenum. The thickening extends for a few centimeters along the pyloric canal, then gradually disappears. The pyloric opening is greatly narrowed and is filled with closely-packed folds of mucous membrane. The thickening is caused by an enormous hypertrophy of the circular layer of muscle fibers. An element of spasm seems to be added to the hypertrophy, because the persistent vomiting which is the principal symptom of the stenosis does not begin for a week or two. The thickened pylorus can often be felt as a round firm mass. Surgery offers no more dramatic result than in the case of the Fredet-Rammstedt operation, which consists in dividing the hypertrophied muscle down to the mucosa; the vomiting stops as if by magic, and the starved child at once begins to put on weight.

**PYLORIC HYPERTROPHY IN ADULTS.**—Concentric hypertrophy of the pyloric muscle is a fairly common finding in autopsies on adults. This type is believed to develop late in life and is not a persistence of the congenital hypertrophy. It may be symptomless or associated with pain and vomiting and is recognizable in the x-ray film by the presence of a long, thin, pyloric canal. It is to be distinguished from the eccentric hypertrophy which so often develops just caudal to a healed ulcer of the duodenum or pyloric canal.

### ACUTE DILATATION OF THE STOMACH

After an abdominal operation under general anesthesia the stomach may occasionally become very rapidly distended until it reaches an enormous size. The condition is likely to be fatal unless treated promptly. At autopsy the stomach may fill the greater part of the abdomen, its wall is very thin, and it contains a very large amount of fluid, although in the early stages the contents are entirely gaseous. The dilatation may stop at the pylorus or may extend as far as the point where the third part of the duodenum is crossed by the superior mesenteric vessels. It is probable that there are two etiological factors: (1) reflex atony of the stomach wall produced by trauma to the abdominal organs similar to the paralysis of the bladder, which may follow operations on the perineum; (2) swallowing of air while the patient is under the anesthetic. In the later stages there is a great outpouring of watery fluid known as gastric succorhea. The use of the stomach tube in the early stage soon relieves the condition.

## CHRONIC DUODENAL ILEUS

Chronic ileus (obstruction) of the duodenum may be caused by narrowing of the angle between the superior mesenteric artery and the aorta through which the third part of the duodenum has to pass. Pressure on the duodenum is produced by the downward pull of the small intestine if it hangs over the brim of the pelvis without resting on the floor of the pelvis. The duodenum may be extremely dilated and its wall thickened. The intestine beyond the obstruction is collapsed. In some cases the stomach may share in the dilatation.

**DUODENITIS.**—Inflammation of the duodenum without ulceration appears to be a distinct entity. Although there is no mucosal defect, the submucosa and muscularis are infiltrated with leucocytes and lymphocytes, and show congestion and edema. Similar lesions are found in the neighborhood of a chronic ulcer. The serosal surface is congested and may be stippled. The symptoms are often similar to those of ulcer, and there may even be hemorrhage. The lesion may involve the ampulla of Vater and obstruct the passage of bile into the duodenum, thus producing an obstructive jaundice which may easily be mistaken for that caused by cancer of the head of the pancreas.

## DUODENAL DIVERTICULA

Roentgen-ray studies have shown that diverticula of the duodenum are much commoner than used to be thought. Two types may be recognized, primary and secondary. A *primary* diverticulum usually arises from the second part of the duodenum, sometimes from the first part, rarely from the third part. It springs from the inner and posterior aspect of the bowel along the line of entrance of the vessels which weaken the wall. There is a herniation of the mucosa through the muscular coat, and the sac thus formed may be as small as a pea or as large as a plum. It may be single or multiple. It occurs in middle and late life. Often discovered accidentally, it may give rise to no symptoms, but when large it may cause dyspepsia, probably from pressure. *Secondary* diverticula are secondary to a duodenal ulcer, so that they occur in the first part of the duodenum. There may be bulging of one or both sides of a healed scar due to traction. The condition is of no clinical significance.

## ADDITIONAL READING

- Adenomyoma of Stomach.** STEWART AND TAYLOR: *J. Path. and Bact.*, 1925, **28**, 195.  
**Alcoholic Gastritis.** BERRY: *J. A. M. A.*, 1941, **117**, 2233. GRAY AND SCHINDLER: *J. A. M. A.*, 1941, **117**, 1005.  
**Carcinoma of Duodenum.** DEEVER AND RAYDIN: *Am. J. Med. Sci.*, 1920, **159**, 469.  
**Carcinoma of Stomach.** BONNE: *Am. J. Cancer*, 1935, **25**, 811. WALTERS, *et al.*: *Arch. Surg.*, 1943, **46**, 939; *Carcinoma and Other Malignant Lesions of the Stomach*, Philadelphia, 1942. WELLS, *et al.*: *Am. J. Cancer*, 1938, **33**, 223.  
**Curling's Ulcer.** HARTMAN: *Ann. Surg.*, 1945, **121**, 54.  
**Duodenal Diverticula.** COLE AND ROBERTS: *Surg., Gynec. and Obst.*, 1920, **31**, 376.  
**Experimental Production of Gastric Cancer.** STEWART AND LORENZ: *J. Nat. Cancer Inst.*, 1949, **10**, 146.  
**Gastritis.** FABER: *Lancet*, 1927, **2**, 901. HENNING: *Die Entzündung des Magens*, Leipzig, 1934.  
**Incidence of Gastric and Duodenal Ulcer.** ALSTED: *Studies on the Changing Incidence of Peptic Ulcer of the Stomach and Duodenum*, London, 1939.

- Leather-bottle Stomach.** WYARD: Surg., Gynec. and Obst., 1925, 40, 449.
- Linitis Plastica.** SAPHIR AND PARKER: Surg., Gynec. and Obst., 1943, 76, 206.
- Neurogenic Factors in Gastric Ulcer.** BOLES AND RIGGS: J. A. M. A., 1940, 115, 1771.  
CUSHING: Surg., Gynec. and Obst., 1932, 55, 1.
- Peptic Ulcer.** ASKANAZY: Virchows Arch. f. path. Anat., 1921, 234, 111; 1924, 250, 370.  
BERGSMA: Arch. Int. Med., 1931, 47, 144. CAYLOR: Ann. Surg., 1927, 86, 905. DORAN: Lancet, 1951, 1, 199. DRAGSTEDT, *et al.*: Gastroenterology, 1944, 3, 450. HEBBEL: Am. J. Path., 1943, 19, 43. HURST AND STEWART: Gastric and Duodenal Ulcer, London, 1929. LINDAU AND WULFF: Surg., Gynec. and Obst., 1931, 53, 621. SOMERVELL: Brit. J. Surg., 1942, 30, 113.
- Phlegmonous Gastritis.** CUTLER AND HARRISON: Surg., Gynec. and Obst., 1940, 70, 234.
- Polyposis.** BRUNN AND PEARL: Surg., Gynec. and Obst., 1926, 43, 559.
- Relation of Ulcer to Cancer.** DIBLE: Brit. J. Surg., 1925, 12, 666. MORLEY: Lancet 1923, 2, 823. NEWCOMB: Brit. J. Surg., 1932-33, 20, 279.



## THE INTESTINES

## ENTERITIS

ENTERITIS means inflammation of the intestine (*enteron*, intestine). The term may be used in this sense, but as colitis signifies inflammation of the large bowel, enteritis is often limited to inflammation of the small bowel. Enteritis is usually a catarrhal inflammation. It may be ulcerative. The term membranous or diphtheritic inflammation is applied to those cases in which a definite layer of necrotic mucosa and fibrin is formed.

Acute enteritis may be produced by: (1) indigestible and irritating foods, (2) food poisoning, (3) chemical poisons, and (4) food deficiencies. So-called food poisoning is really due to the action of pathogenic bacteria contained in the decomposing food, the most important being *Bacillus enteritidis* (Gärtner) and the paratyphoid group. Many chemical poisons may irritate the intestine. Arsenic and mercury cause inflammation of the lower part of the ileum and most of the large bowel, apparently being excreted lower down after having been absorbed. In infective fevers, septicemia, and uremia enteritis may be present.

LESIONS.—The mucous membrane is swollen, edematous, covered with a slimy exudate, and flecked with red spots. It is seldom red throughout except in the severe inflammation produced by chemical poisons. The lymphoid follicles, particularly in children, are often swollen and the overlying mucosa may be shed off so as to form little, clear-cut shallow ulcers (follicular ulcers). *Microscopically* the change is confined to the mucosa and submucosa which are infiltrated with round cells and show marked edema. Polymorphonuclears are present in the more acute stages. The surface epithelium is degenerated, but in the intestine as in the stomach it is always difficult to separate antemortem from postmortem degenerative changes.

## BACILLARY DYSENTERY

Bacillary dysentery and amoebic dysentery are two entirely different diseases, and the only justification for grouping them under one heading is historical usage. Bacillary dysentery is very common in tropical countries, but is also found in the temperate zone, especially where men are crowded together under poor hygienic conditions. It is thus a great destroyer of armies in the field, it appears in large mental hospitals in both endemic and epidemic form, and it is the chief cause of the acute enteritis of children associated with the passage of pus and blood.

**SYMPTOMS.**—Dysentery is a diarrhea characterized by the presence of mucus, pus, and blood in the stools (a "bloody flux"), and accompanied by straining and tenesmus. The infection is an acute one lasting several weeks, but the condition may become chronic or there may be periodic recurrences. In addition to the local symptoms the patient shows evidence of the action of a powerful diffusible toxin and dies of toxemia.

**LESIONS.**—Bacillary dysentery resembles diphtheria in that the bacilli remain localized, do not penetrate the tissues at first nor invade the blood stream, and produce local necrosis and distant damage by the means of their exotoxins. When an ulcer has been produced the bacilli may penetrate into the deeper parts of the wall. The disease is an acute colitis, but the lower part of the ileum may also be involved. The toxins cause an acute inflammation of the wall of the bowel, patches of the mucous membrane become necrotic, are converted into sloughs, and when these separate, ulcers are formed. The surface of the ulcer may become covered by an inflammatory exudate consisting of fibrin and polymorphonuclear leucocytes which together with the necrotic material, may form a false membrane (diphtheritic inflammation). The ulcers seldom penetrate the muscularis mucosæ, but sometimes they may reach the serous coat and perforate. The ulcers are clear-cut, and have not the undermined edges seen in the amoebic form. There may be many small ulcers, or they may coalesce to form a few very large ones. The mucosa between the ulcers may become papillomatous.

*Microscopically* the wall of the bowel is infiltrated with polymorphonuclear leucocytes. There is marked edema and thickening of the submucosa. Large numbers of Gram-negative bacilli are present in the floor of the ulcer. *Healing* takes place by the formation of granulation tissue which becomes covered by a simple epithelium without glands. If the ulceration is superficial there is little scarring, but when deep there may be much scar formation with the production of marked stenosis of the bowel.

**THE RELATION OF SYMPTOMS TO LESIONS.**—The pain, tenesmus, and diarrhea are due to the acute inflammation of the large bowel. The pus and blood in the stools are the result of the ulceration. Mucus may be abundant, especially in the chronic cases. As the disease is a local one there are no signs of septicemia, such as acute splenic swelling. The toxins may act on the nervous system, producing a peripheral neuritis, and on the joints causing a painful effusion. Liver abscesses are very rare (cf. Amoebic dysentery).

### AMOEBCIC DYSENTERY

The amoebic form of dysentery is caused by *Entamoeba histolytica*, a protozoal parasite. It is gradual in onset and more protracted in its course than the bacillary form, sometimes lasting for months or years. The incubation period varies from ten to ninety days. Although primarily a disease of the tropics there is a growing incidence of infestation with the parasite in temperate regions, and serious localized epidemics are becoming more common. These can usually be traced to cooks and other handlers of food (in hotels, etc.) who are either carriers of the amoeba or suffer from the disease in a mild form. An infected water supply is another source of danger. A remarkable outbreak occurred in Chicago, June 1933–June 1934, during which period there were 1409 cases (98 deaths), 75 per cent of whom had

contact with one or other of two hotels. From this center the disease was scattered over 400 cities, 43 states and 3 Canadian provinces. At first it was thought to be a carrier epidemic, as the incidence of carriers among the employees of the two hotels was 37.8 and 47.4 per cent, but eventually it was traced to water infection, an overhead sewer leaking into the drinking water supply. The parasite may be present in two forms, one active or amœboid (trophozoite), the other encysted. The latter is developed when conditions for growth are not favorable, and is the only infective form, for the active form is destroyed by the HCl as it passes through the stomach. The cysts may live outside the body for weeks in moisture and shade. The active form is detected by direct microscopic examination of a warm stool preparation, but the cysts are shown up best when such a preparation is stained with a mixture of iodine and eosin. The cysts do not occur in the tissues, nor are they passed in any numbers in the acute dysenteric stage (diarrhea); they are generally found only in semiformed or formed stools. For doubtful encysted forms a fixed smear should be stained with iron hematoxylin. In acute cases the stool contains the active form, while in chronic cases and carriers cysts are to be expected. The features by which the two forms may be recognized are described in Chapter 8.

**LESIONS.**—When a cyst is swallowed in food or water it breaks up in the lower part of the small bowel and liberates a single amœba with 4 nuclei. These divide into 8, and 8 small amœbæ are formed. When they reach the large bowel they penetrate the lumen of the glands and, destroying the epithelium with which they come in contact by proteolytic enzymes, they penetrate the deeper tissues. No lesion is produced in the bowel



FIG. 254.—*Amœba histolytica* in wall of bowel.  $\times 400$ .

unless the amœbæ colonize actively; they merely enter the portal venules and to a lesser extent the lymphatics. If they colonize in the submucosa, the result is dysentery. The parasites spread out in this coat and set up a colliquative necrosis by virtue of the proteolytic ferment which they produce. All this is quite different from bacillary dysentery where the organisms remain on the surface and by means of their diffusible toxins excite a suppurative inflammation instead of a quiet necrosis in the underlying tissue. The mucosa overlying the necrotic areas also dies and is cast off as a slough, so that ragged ulcers are formed. These ulcers have deeply undermined edges, because the submucosa is more extensively involved than the mucosa. The mucosa between the ulcers appears remarkably healthy because no diffusible toxin is at work. The ulcers are deeper than in the bacillary form, and the floor is often formed by the thickened peritoneum.

The *microscopic picture* is one of quiet necrosis with little or no inflammation. Large numbers of amœbæ can be seen in the wall of the bowel. They digest the surrounding tissue by means of their proteolytic ferment, so that they frequently lie in small spaces (Fig. 254), but they appear to excite comparatively little reaction. Any inflammatory cells in the floor of the ulcer are mononuclear in type. At a later date secondary infection may occur and this may cause some suppuration. The amœbæ penetrate the portal venules and can be seen lying within the lumen, so that they readily pass to the liver.

*Liver abscess* is thus a common complication of amœbic dysentery. Although the lesion is commonly known as solitary abscess, it is multiple in over 50 per cent of the cases, being more frequent in the right lobe. There may be a few large or numerous small abscesses. The lesions are really not true abscesses, but are formed by the liquefaction necrosis of the liver cells produced by the digestive ferment of the amœbæ. The abscess may rupture into the abdominal cavity, or through the diaphragm into the lung, the patient expectorating a brown "anchovy sauce" material containing many amœbæ.

**BACILLARY AND AMŒBIC DYSENTERY COMPARED.**—The chief symptom of dysentery—diarrhea with blood, mucus and pus in the stools—is the same in both forms. Bacteriological and immunological tests are of value in differentiating the two forms, but a rapid and useful method is the cytological examination of the stools, the type of cell depending on the histological reaction in the lesions. It will be remembered that there are three types of necrosis: lysis, pyknosis, and karyorrhexis. In *bacillary* infections cellular lysis is marked, the result being "ghost cells" from the macrophages and "ring nuclei" from the polymorphonuclear leucocytes. About 90 per cent of the cells are polymorphonuclears, but this loses its value from the fact that when amœbic lesions become secondarily infected the exudates may be purulent. The most important cells are the macrophages and their ghost forms. Unfortunately these may bear a striking resemblance to amœbæ, and be a cause of mistaken diagnosis except in the hands of an expert, as happened in the epidemics both at Gallipoli and on Corregidor. In pure amœbic infections the cells are few in number and are mainly mononuclears. They present either a "mouse-eaten" appearance due to the action of the digestive enzyme on parts of the cytoplasm, or "pyknotic bodies" from the nuclear fragments. Large numbers of red blood cells are always present in addition to the amœbæ. Charcot-Leyden crystals are characteristic of amœbic dysentery, and are not found in the bacillary form.

Some of the principal points in which bacillary differs from amœbic dysentery are summarized as follows:

	<i>Bacillary dysentery</i>	<i>Amœbic dysentery</i>
1. Type of lesion	Suppurative	Necrotic
2. Depth of ulcer	Generally shallow	Generally deep
3. Edge of ulcer	Sharp	Undermined
4. Intervening mucosa	Inflamed	Normal
5. Organisms in lesions	<i>Bacillus dysenteriae</i>	<i>Entamoeba histolytica</i>
6. Cytology of stools	Polymorphonuclears	Mononuclears
7. Liver abscess	Rare	Common

## IDIOPATHIC ULCERATIVE COLITIS

Bacillary and amoebic dysentery are comparative rarities in civilian practice in non-tropical countries. The puzzling condition known as *chronic ulcerative colitis*, on the other hand, is common. It is called idiopathic because the etiology is obscure. The cause may be negative rather than positive in character, something lacking in the patient or the patient's bowel, possibly a food deficiency. In many cases there seems to be a strong psychogenic factor. It has been said that the sorrow which has no vent in tears may make other organs weep. Unexpressed anger and resentment may be reflected in the colon by hyperemia and hypermotility. Under the best hygienic conditions the patient may recover for a time and remain well, but when he is subjected to strain, overwork and worry the symptoms and lesions return once more. The disease is essentially chronic, continuing for years, although marked by remissions and exacerbations, but occasionally it may run an acute course. In one of my cases the entire illness was of five weeks' duration, yet at autopsy the lesions were unbelievably extensive.

The earliest changes are in the rectum and sigmoid, spreading upward to the splenic flexure. These are the parts of the bowel supplied by the sacropelvic portion of the parasympathetic system, the remainder of the bowel being supplied by the vagus. The mucolytic enzyme, *lysozyme*, appears to be under nervous control and is greatly increased in amount as the result of emotional stimuli. This enzyme liquefies the mucus which normally protects the intestinal mucosa, so that excessive destruction of this protective layer will expose the mucosa to the action of bacteria and of pancreatic tryptic enzyme. In ulcerative colitis the lysozyme is enormously increased. It would appear that in this disease emotional stimuli to the rectum and sigmoid cause local overproduction of lysozyme with breakdown of defence and exposure of the mucosa to tryptic enzymal digestion (Portis). This would link the diffuse lesions of colitis with the localized lesions of peptic ulcer. During periods of stress marked by feelings of humiliation with anxiety, resentment and hostility which are unexpressed and repressed there is pronounced and sustained elevation of the lysozyme compared with normal persons (Grace *et al.*). These high values precede exacerbation of symptoms with bleeding. Without risking undue dogmatism it may be said that emotional stimuli from the hypothalamic area and increased local production of lysozyme may well play a part in the pathogenesis of the lesions of ulcerative colitis. Treatment has to be directed to the mind as well as to the colon.

The dominant, constant, and distressing symptom is diarrhea, with blood, pus, and mucus in the stools. Secondary anemia and loss of weight are common. The roentgen rays show a hyperactive colon with loss of the normal haustrations (pipe-stem colon). With the sigmoidoscope ulcers are seen scattered over the reddened mucous membrane of the sigmoid and rectum. The ulcers are covered with mucus and bleed at the slightest touch, so that it is no wonder that blood in the stools is common.

The ulcers which form the principal lesion are usually confined to the colon and rectum. In fatal cases the entire large bowel may be covered

with ulcers which vary from tiny erosions to ulcers several inches in diameter. Sometimes they are arranged along the line of the *tænia coli*. The ulcers are usually quite superficial, involving only the mucosa, but the muscular coat may also become necrotic, so that occasionally the base

may come to be formed by the peritoneum with great danger of perforation. The intervening mucosa is often swollen and edematous so that polypoid masses project from the surface (colitis polyposa). One of these polypi may become malignant. The wall of the bowel may be very friable, so that the sigmoidoscope has to be used with care. The mesenteric lymph nodes are sometimes enlarged and inflamed.

The *microscopic appearance* is that of a chronic bacillary dysentery. At the site of the ulcer the mucosa has disappeared, but the submucosa is much thickened and infiltrated with round cells and leucocytes. The muscular coat is sometimes involved, and the peritoneum over the deep ulcers is thickened. The mucosa between the ulcers is thick, congested, and edematous. *Healing* occurs with very little scarring, so that there is no danger of stricture of the bowel.

*Lesions of other organs* are often found at autopsy. In some 40 per cent of cases necrotic and degenerative lesions are present in the *liver* (Kimmelstiel). These are probably metabolic in origin due to the diarrhea. In the *kidney* there may be glomerular and tubular changes (Jensen *et al.*). Glomerular endothelial proliferation

is frequent and may cause obstruction to blood flow through the capillaries. Large vacuoles of undetermined nature are sometimes present in the tubular endothelium. In the *pancreas* there may be chronic interstitial inflammation, fibrosis and dilation of acini, the latter perhaps related to the marked protein deficiency (Ball *et al.*).



FIG. 255.—Ulcerative colitis. Ulcers are most marked along line of *tænia coli*.

**UREMIC ENTERITIS.**—In uremia there may be severe diarrhea, with purulent or bloody stools. The lesions are ulcerative and necrotizing. There are numerous ulcers in the large bowel and the lower part of the small bowel, particularly in the lymphoid tissue. The enteritis is associated in some way with urea retention, for similar lesions can be produced in dogs by the intravenous injection of urea.

**Antibiotic Enteritis.**—As a result of indiscriminate antibiotic therapy, especially the use of broad spectrum antibiotics such as chloromycetin, aureomycin and terramycin, resistant strains of staphylococci may invade the bowel from the nose and throat and multiply rapidly. These organisms are rarely found in the stools of normal persons, and never in large numbers. Unfortunately the incidence of resistant strains of staphylococci in the bowel appears to be increasing as the result of broad spectrum antibiotics which displace the normal Gram-negative inhabitants of the bowel. This increase is only observed in large institutions such as hospitals, where the mass effect of the newer therapy has room to operate, and where the personnel become carriers of the resistant stains.

This change in the intestinal bacterial flora is accompanied by an illness which may end fatally and which is marked by severe diarrhea together with excessive fatigue and exhaustion like that which accompanies influenza (Dearing and Heilman). There is an acute desquamative and membranous enterocolitis with enormous masses of hemolytic staphylococci in the exudate and membrane (Terplan). Large numbers of staphylococci are present in the stools, in distinction to the condition known as pseudo-membranous colitis which also may complicate antibiotic therapy but in which no staphylococci are found in the stools (Reiner *et al.*). These lesions are not specific, and resemble those of uremic and arsenical colitis and of starvation. There is a very marked female sex incidence.

The explanation of these disturbances of bowel function and structure is not easy. The profound change in the character of the bacterial flora must play a major role. The condition has been called staphylococcal enteritis, but there is no proof that the staphylococci produce toxins. The absence of the normal Gram-negative flora may be even more important than the presence of abnormal bacteria. In the healthy bowel there is not only a symbiotic balance between the several microorganisms, but a homeostatic balance between the products of these organisms and the tissues with which they come into contact. Such a balance cannot be upset with impunity. Finally there is the possibility of a nutritional deficiency produced by the inhibition of the normal bacterial flora of the bowel which are necessary for the processing of food (Zamcheck *et al.*). Primary nutritional disorders such as pellagra and sprue are characterized by intestinal symptoms. The intestinal mucosa is metabolically one of the most active tissues in the body and, at least in the rat, its cells are replaced every two or three days, so that it reflects disturbances of nutrition promptly by functional and structural change. It is known that such changes are produced by adrenal cortical hormones and growth antagonists such as aminopterin as well as by aureomycin and terramycin. It seems reasonable to suggest, therefore, that the disturbances under consideration are at base nutritional, probably

owing to the absence of the normal bacterial flora of the bowel. Sex hormones may play some part by interfering with enzyme activity.

### TYPHOID FEVER

Typhoid fever may be regarded as an intestinal disease, for the more obvious lesions are the ulcers of the bowel and it is they which give rise to the dangerous complications, hemorrhage and perforation. But it is really a general infection of the whole body, though the initial lesions are in the bowel, so that it is considered in connection with the Infectious Diseases.

### CHOLERA

Cholera is an acute inflammatory condition of the intestine produced by Koch's spirillum and occurring mainly in tropical countries. Infection is due to drinking polluted water. The wise Chinese are the only Orientals who do not suffer from cholera; they use boiled water and cooked food, they drink tea and eat hot rice. Like bacillary dysentery it is an example of a purely local infection, the other organs merely showing the effects of toxemia. Both the large and small intestine are much distended with watery fluid like thin barley soup. As a result of the constant passage of these watery stools (rice-water stools) the patient becomes extremely dehydrated. The entire length of the mucous membrane is intensely congested, being of a deep red color. Hemorrhages are common. Unlike typhoid and dysentery, there is no ulceration. The epithelium covering the mucosa is shed off so that a raw surface is left, but the mucosa itself is not destroyed, although infiltrated with inflammatory cells. The lymph follicles are swollen and the mesenteric lymph nodes may be necrotic. The spirilla are found in the intestinal contents and in the bile.

The other organs show the effect of acute toxemia (cloudy swelling, focal necrosis). There is acute splenic swelling. A striking feature is the extraordinary degree of rigor mortis, the arms and legs being as stiff as iron rods. Inoculation against the disease is now of great value. In a barracks of 180 men only 4 were uninoculated, and 3 of these were the only ones to get the disease.

### TUBERCULOSIS OF THE INTESTINE

The infection is usually secondary to pulmonary tuberculosis. Before the days of pasteurization of milk primary infection due to drinking tuberculous milk from infected cows was very common, particularly in children. The secondary type of lesion is due to massive infection from sputum which has been swallowed. A few bacilli do not seem to produce a recognizable lesion. For this reason the condition is usually associated with the presence of large cavities. Ulceration of the bowel is the commonest complication of pulmonary tuberculosis, and is found in from 50 to 80 per cent of the cases which come to autopsy; but it is by no means only a terminal occurrence.

The method of infection appears to be as follows: a massive dose of bacilli is swallowed, and the organisms pass into the tubular glands of the intestinal mucosa, where an inflammatory exudate is produced in the depths of the gland. The bacilli are then carried through the epithelial lining



by phagocytic cells, and thus reach the submucosa where they give rise to the usual tuberculous lesions. The overlying mucosa may now be cast off with the formation of an ulcer, or it may remain intact so that the bowel may be tuberculous though not an ulcer can be seen. The bacilli may be carried from the submucosal lesion to the mesenteric lymph nodes which drain that segment of the bowel, and there produce caseous lesions. Mesenteric lymph node tuberculosis indicates intestinal tuberculosis but not necessarily intestinal ulceration.

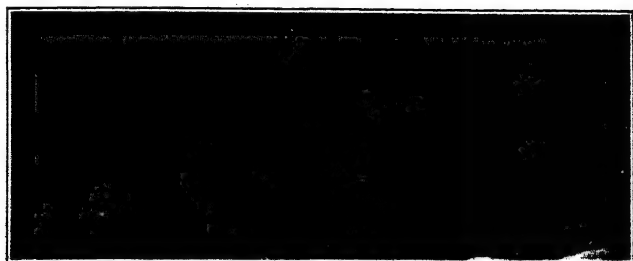


FIG. 256.—Tuberculosis of the bowel. There are two shallow tuberculous ulcers.



FIG. 257.—Tuberculous ulcer of bowel showing undermined edge and areas of necrosis in the base.  $\times 15$ .

**SYMPTOMS.**—The symptoms are general and local. The general symptoms are those of pulmonary tuberculosis, i.e., loss of weight, asthenia, etc. Every case of pulmonary tuberculosis which does poorly but with no increase in the physical signs should suggest intestinal ulceration. The local symptoms are abdominal pain, diarrhea, and the presence of pus and blood in the stools.

**LESIONS.**—The first lesions appear in the ileocecal region, although at autopsy they may be scattered over a wide area. From this site of election the disease spreads up and down. As is usual with tuberculosis, the earliest

lesions are in the lymphoid tissue and appear as small gray tubercles in the Peyer's patches and solitary follicles, which become yellow from caseation, soften, and break down (Fig. 256). The overlying mucosa undergoes necrosis and is cast off, the underlying caseous tissue is discharged, and an *ulcer* with ragged undermined edges is formed (Fig. 257). In the small bowel the ulcer may extend as far as the peritoneum, but in the large bowel it is shallower and seldom penetrates the muscularis. Small tubercles can be seen on the serous coat, or they may be covered up by a plastic



FIG. 258.—Tuberculosis of bowel.  $\times 100$ .



FIG. 259.—Regional ileitis.

exudate. The overlying peritoneum is usually thickened so that perforation is uncommon. The ulcer is supposed to spread transversely across the bowel (girdle ulcer), but quite often it lies in the long axis, especially when it is confined to a Peyer's patch. The *mesenteric lymph nodes* are enlarged and may be caseous. Extension of the inflammation outside the bowel leads to *adhesions*, and these by contracting produce acute *kinks* of the bowel which are a common cause of intestinal obstruction. The *microscopic picture* is one of tuberculous foci with epithelioid cells and lymphocytes, giant cells, and caseation (Fig. 258). Enderteritis obliterans is common, and this usually prevents a large hemorrhage from occurring.

*Healing* is common, especially with modern methods of light treatment. The mucosa may be completely restored when the ulcer is shallow, and even deep ulcers become filled with granulation tissue and covered by a simple epithelium. But when destruction of tissue is extensive, cicatrization is correspondingly great, and if the ulcer is of the girdle type stenosis may result. These strictures are often multiple. Serious obstruction is much more likely to be due to kinks of the bowel produced by adhesions than to cicatricial stenosis, but in the primary lesions seen in children the cicatrices may lead to a marked degree of obstruction.

*Perforation* of a tuberculous ulcer may be complete or incomplete. *Complete* perforation in the general peritoneal cavity occurs in the small intestine where the ulcers are deeper, but it is not common owing to the thickening of the peritoneum. *Incomplete* perforation, which is much commoner, is seen in the large bowel, especially in the right iliac fossa, where it gives rise to a fecal abscess walled off by dense adhesions.

THE RELATION OF SYMPTOMS TO LESIONS.—The *general symptoms* bear no relation to the lesions. The *pain* is not caused by the ulcers, for these are insensitive. It is due to spasm of the bowel, involvement of the peritoneum, or tuberculous lymphadenitis. The *diarrhea* is related to the hypermotility of the bowel which forms a striking feature of the roentgen-ray picture rather than to the ulceration. The hypermotility seems to depend in turn on inflammatory and degenerative lesions of the myenteric plexus of Auerbach. The site of the disease is also related to the diarrhea; lesions of the small bowel are generally associated with constipation, those of the large bowel and especially the descending colon with diarrhea. *Occult blood* in the stools and *pus* in small amount are due to the intestinal ulceration.

**Regional Ileitis.**—In 1932 a nonspecific chronic inflammatory condition of the small bowel was described by Crohn and his associates under this name. The site of election is the final 12 or 18 inches of the ileum, ending abruptly at the ileocecal valve (Fig. 259), so that it has been called terminal ileitis, but other segments of the small and even the large intestine may be involved. It may indeed be limited to the rectum. For this reason the term Crohn's disease is in some ways to be preferred. The affected part is thick, heavy, and reddened. The mucosa presents a lumpy thickening, to which the descriptive name of cobblestone appearance has been given. The lumen is narrowed, the intestine above becoming dilated. The mesentery is stiff and greatly thickened, and adhesion of the bowel to neighboring structures (bowel and abdominal wall) is followed by slow perforation and fistula formation. *Microscopically* the picture is usually singularly nonspecific, consisting of marked edema of the submucosa and to a lesser degree of the other coats, together with lymphocytic infiltration and a varying amount of ulceration. One of the most remarkable features is the patchiness of the lesions. In some cases there is a lymphadenoid hyperplasia of the submucosa with the formation of non-caseating giant-cell systems resembling those of Boeck's sarcoid (Hadfield) (Fig. 260). In the later stages ulceration may obscure and obliterate the primary lesion in the submucosa, but the giant-cell systems may still be found in the regional lymph nodes. The outstanding clinical features are a mass in the right iliac region, diarrhea and fever. The disease may begin with an

attack like appendicitis, thus resembling actinomycosis of the bowel. The etiology is obscure.

### ACTINOMYCOSIS OF THE INTESTINE

Actinomycosis of the bowel usually occurs in the cecum or appendix, but occasionally in the pelvic colon. A mass of granulation tissue is formed in the submucosa, followed by ulceration of the mucous membrane. The cecum shows the same great thickening as in the hyperplastic form of tuberculosis, but suppuration occurs and the mass is converted into a nest of abscesses. The disease may spread to the abdominal wall with the formation of a sinus from which pus is discharged containing the characteristic sulphur granules in which the ray fungus is readily demonstrated. The liver may become involved by way of the portal vein, and is eventually riddled with abscesses. Actinomycosis of the cecum is apt to be mistaken clinically for carcinoma.

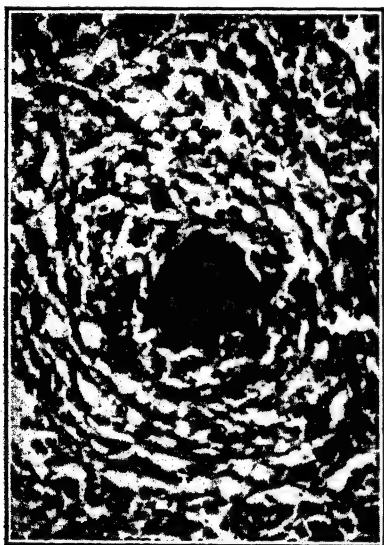


FIG. 260.—Tuberculoid lesion in Crohn's disease.  $\times 192$ .



FIG. 261.—The obstructive element in acute appendicitis. Fibrous stenosis of proximal end, dilatation and thinning of distal half, and occlusion of lumen by a fecolith.

### APPENDICITIS

In discussing the general features of appendicitis it is convenient to consider the acute form. It must be realized that acute does not necessarily mean severe. Acute inflammation of the appendix slight in degree is very much commoner than the severe variety.

**ETIOLOGY.**—The etiological factors are exciting and predisposing. The two great *exciting* factors are obstruction and infection. It is becoming more and more apparent that the former is the dominant factor. Wangenstein and Bowers found that complete obstruction of the infected cecal

appendage in the dog always results in inflammation, whereas if there is infection without obstruction or obstruction without infection no inflammation develops. Pressure-distention is an exciting factor of first importance; increased pressure within the lumen for six to twelve hours causes inflammatory changes in the walls. There is a sphincter-like mechanism at the base of the appendix which makes it a potential closed loop, and is probably responsible for the formation of concretions. Wangenstein and Bowers found that when a needle was passed through the tip of the uninfamed human appendix at operation and attached to a column of water, not a drop escaped into the cecum with a pressure of 40 cm. of water. This suggests that a sphincter-like mechanism exists at the proximal end of the appendix which may be stimulated to contract by increase of pressure within the lumen as well as through the extrinsic nerves. The symptoms of appendicitis can be produced by tying the base of the appendix and slowly distending the lumen by injecting saline solution. Obstruction, then, may be caused not only by the easily recognized concretion (Fig. 261), but by contraction of the sphincter, as well as by swelling of the abundant lymphoid tissue in the wall, previous fibrosis of the proximal end, acute kinking by a band of old adhesions or by a congenital fold. Wangenstein and Bowers found obstruction in 72 per cent of cases of acute suppurative appendicitis and in 100 per cent of gangrenous appendicitis (80 per cent concretions). In most cases, then, obstruction seems to be a much more important initial factor than infection. The acute attack has been likened to a knock at the door saying, "Let me out." As the result of obstruction the lumen becomes distended, the intraluminal pressure increased and the venous return interfered with, so that the vessels rupture, hemorrhage occurs, the wall is poorly oxygenated and invaded by bacteria, the swelling increases, and perforation is the end-result. There is no doubt that a blow on the abdominal wall may occasionally precipitate an acute attack of appendicitis. As might be expected, mild cases are much more likely to have had multiple attacks, because the obstruction is slight and is overcome spontaneously, so that the patient can go on to another attack. The severe (gangrenous) cases have few previous attacks, because the obstruction can only be overcome by perforation of the appendix; it is natural that fecoliths causing complete obstruction should be common in these cases.

The infecting organisms appear to invade the mucosa from the lumen. They are probably the normal inhabitants of the appendix. Streptococci and *B. coli* are most commonly found, often in combination. The streptococcus is probably the chief infective agent, for the inflammation tends to spread throughout the organ in the same manner as streptococcal infections elsewhere. It is probable that in exceptional cases infection may be by the blood stream, as when acute appendicitis occurs in the course of acute tonsillitis or septic sore throat.

The *predisposing causes* are indefinite. The disease is commonest in the second and third decades; it is rare in infancy and old age. Previous damage to the appendix with fibrosis predisposes to future attacks. The disease is common in highly civilized countries and urban communities, but rare in remote rural districts and among primitive peoples. During the nine

years that McCarrison practised among the hill tribes of the Himalayas he never saw a case of appendicitis. Natives who live on a diet abundant in cellulose are immune from the disease, but when they adopt the diet of civilization they lose that immunity. These and many other similar facts suggest that habits of life, and in particular modes of diet such as meat-eating, are of importance in predisposing toward appendicitis.

It is very difficult to hit on a classification of appendicitis which will be satisfying both to the pathologist and the clinician. The pathologist is primarily interested in reporting on appendices which have been removed by the surgeon. These may be divided into the following groups: acute appendicitis, healing appendicitis, fibrosed appendix, and normal appendix. The last need not be considered further.



FIG. 262.—Acute appendicitis. Small mucosal abscess rupturing into the lumen.  $\times 26$ .

*Acute Appendicitis.*—Acute inflammation of the appendix may take a variety of forms. It may be mild with correspondingly mild symptoms, a condition to which the clinician is fond of applying the quite unjustifiable term *catarrhal appendicitis*. A patient may suffer from a succession of mild attacks, and it is to these recurring attacks that the clinician applies his favorite name of *chronic appendicitis*. In other cases the inflammation is severe and purulent. These may be called *acute suppurative appendicitis*. Gangrene may be present, particularly when there is an element of obstruction; these are cases of *gangrenous appendicitis*.

In *acute suppurative appendicitis* the infection seems to begin at the bottom of one of the crypts, where a small focus of suppuration is formed

in the mucosa (Fig. 262). The organisms apparently do not readily spread through the mucosa, because that coat may be apparently normal apart from one or two points of abscess formation although the rest of the appendix is acutely inflamed. The spread takes place in the loose submucosa, and from there through the muscularis along the line of the penetrating vessels to the subserous coat, where it again becomes diffuse. In looking for evidence of inflammation, therefore, attention should be directed to the submucous and subserous layers. By the time the appendix is removed the muscularis and peritoneal surface are usually also inflamed.

The appendix is swollen and elongated, bright red in color, with dilated subperitoneal vessels and a fibrinous or purulent exudate (sometimes very slight) on the surface. There may be yellow spots on the surface indicating the beginning of an abscess. The tip is usually swollen, and the whole process is likely to be more marked in the distal than the proximal part. When the appendix is opened the mucosa is seen to be swollen and very congestive. The surface is granular or warty. Superficial erosions are common, but there may also be ulcers which penetrate to the submucous coat and sometimes to the peritoneum. The lumen may be narrowed owing to swelling of the mucosa, but if that layer is destroyed it may be dilated and filled with pus.

*Microscopically* all the coats are congested, edematous, and infiltrated with polymorphonuclear leucocytes, but the mucous membrane may show little or no infiltration. The normal cellularity of this membrane makes it difficult to be certain of slight changes in the number and kind of cells. Eosinophils may be very abundant, especially when the acuteness of the inflammation is passing off. Necrosis of the mucosa is common, and masses of dead membrane may be cast off, thus forming ulcers especially at the points where the lymph follicles approach the surface. There may be hemorrhages in the mucosa which often leave a permanent pigmentation. The mesentery of the appendix shares in the inflammation, being thickened, edematous, and infiltrated with polymorphonuclear leucocytes. Thrombosis of the vessels may occasionally give rise to abscess formation in the liver (portal pyemia).

*Gangrenous appendicitis* is one variety of acute suppurative appendicitis. There is death and putrefaction of the tissues of the appendix due to interference with the blood supply. The gangrene is often local, appearing as a green or black patch at the distal end, often at the tip. (Plate XII.) A concretion which is sometimes quite hard is often found at the site of gangrene, and has no doubt played an etiological part by pressing on the stretched and inflamed wall.

*Perforation* may occur at any stage of acute appendicitis, but is commonly associated with gangrene. The ulceration of the mucosa already described may penetrate the muscular and serous coats causing perforation. A fecal concretion is often present at the site of the perforation, and evidently plays a part in its production. It may escape into the abdominal cavity. If the perforation occurs into the open peritoneal cavity *general peritonitis* will at once be caused by the flooding of the membrane with septic material. Often, however, the inflamed part of the appendix is surrounded by a layer of omentum which becomes adherent to it before perforation has time to

occur. In this case a *local appendicular abscess* will be formed, and there may be no infection of the general peritoneal cavity. The abscess may involve the anterior abdominal wall, and when it is opened a *fecal fistula* may result, through which fecal matter is discharged from the appendix on to the abdominal wall.

*Healing Appendicitis.*—The appendix is often removed a few weeks after an acute attack has passed off. It may be slightly swollen or of normal thickness. The polymorphonuclears in the submucous and subserous coats are replaced by chronic inflammatory cells, chiefly lymphocytes but sometimes with such large numbers of eosinophils that the affected



FIG. 263.—Fibrosis of appendix; inset shows normal thickness of coats. (Boyd's Surgical Pathology.)

part looks red under the low power. The lymphocytes in the subserous coat may have a perivascular distribution, and the general picture may strongly suggest chronic inflammation. Very many appendices which are diagnosed by the laboratory as chronic appendicitis are really examples of healing appendicitis. The inflammation is transient, not chronic.

*Fibrosis of the Appendix.*—The term *chronic appendicitis* is applied by the surgeon to a thickened and fibrosed appendix which he may remove at operation. This is likely to be either the healing stage of acute appendicitis or fibrosis of the appendix resulting from recurring mild acute attacks. It is doubtful if there is such an entity as chronic appendicitis in the sense of a slowly progressive inflammation without acute exacerbations.



## PLATE XII



FIG. 1



FIG. 2

Fig. 1.—Carcinoid Tumor of Appendix Showing the Characteristic Yellow Ring.

Fig. 2.—Gangrenous Appendicitis. The Distal Third is Gangrenous, and is About to Perforate at the Lower Border.

*(Boyd's Surgical Pathology, courtesy of W. B. Saunders Company.)*

Although symptoms such as dyspepsia and discomfort in the right iliac fossa may be relieved temporarily by removal of the appendix, a careful follow-up history will show that these symptoms will eventually recur.

The fibrosed appendix is thickened and rigid. The fibrosis is most marked in the submucous and serous coats (Fig. 263), but if the mucosa has been destroyed, the lumen may be obliterated. Dilated lymphatics in the subserosa may contain collections of lymphocytes, but these are also seen occasionally in normal appendices. In old age the appendix may be pale, withered and shrunken, with obliteration of the lumen, and fusion of the coats into a fibrous mass. This may be regarded as a non-inflammatory atrophy.

Masson has shown that the normal appendix contains a large amount of non-medullated nerve fibers, and that this amount may be greatly increased as the result of inflammation. In the infant plain muscle bundles accompanied by the nerves of Meissner's plexus can be seen to pass inward from the circular muscle coat and outward from the muscularis mucosæ to anastomose in the submucosa and form a "neuromuscular complex." In the adult the presence of lymph follicles makes this arrangement less easily detected. Sometimes the submucosa shows a remarkable hypertrophy of the neuromuscular complex. The mucosa may also be thickened, and may contain numbers of small circumscribed neuromas (neurinomas). These are much more frequent than neuromuscular hyperplasia (Fig. 264). It remains to be seen whether hyperplasia of this nerve tissue may be responsible for symptoms in the right iliac fossa, and whether the term "neurogenic appendicitis" is justifiable.

*Mucocele of the appendix* is a condition in which stenosis of the proximal part results in distention of the distal part with clear mucinous fluid to form a cyst. In rare cases the mucocele may be the starting point of *pseudomyxoma peritonei*, rupture of the cyst being followed by implantation of epithelial cells on the peritoneal surface, and the formation of large mucoid masses like frog's spawn.

In *Graves' disease* there is sometimes tremendous lymphoid hyperplasia of the appendix; the proliferating lymphocytes may wipe out the mucosa, infiltrate the muscular wall, and obliterate the lumen.

In *measles* during the prodromal stage giant cells are found in the germ centers and neighboring lymphatic tissue of the appendix, and in the regional lymph nodes. The giant cells may be 100 microns in diameter, and contain from 50 to 100 nuclei.

THE RELATION OF SYMPTOMS TO LESIONS.—Apart from fever and leucocytosis which are due to the infection, the chief symptoms are nausea, vomiting, and local pain and tenderness. In acute appendicitis the hyperemia and inflammatory exudate cause distention of the organ with stretching of the sympathetic plexus which lies in the outer part of the wall. The stimuli pass to the semilunar ganglia and give rise to nausea, vomiting, and general abdominal pain. The inflammation



FIG. 264.—Neurinoma in fibrosed appendix. (Masson's trichrome stain.)  $\times 50$ .

soon reaches the serous coat, and the inflammation of the *parietal* peritoneum is the cause of the local pain and rigidity. The local symptoms are more severe and more sudden in onset when acute obstruction is a marked feature, because the distention of the appendix is much greater. In the most severe and fulminating cases the local symptoms may be slight except at the very beginning, because the rapidly developing gangrene soon destroys the sympathetic nerve endings.

The problem of so-called chronic appendicitis is much more complex and cannot be discussed here. On purely pathological grounds it does not seem reasonable to suppose that the multitudinous symptoms of "chronic appendicitis" (chronic dyspepsia, vague abdominal pain and tenderness over the appendix are the classical ones) can be caused by fibrotic changes in the appendix. But it is possible that at least in some cases Masson's neuromuscular hyperplasia may represent the anatomical substratum of the symptoms.



FIG. 265.—Carcinoma of the large bowel. There is almost complete obstruction, and above the obstruction the bowel is greatly dilated.

## TUMORS OF THE INTESTINES

**Carcinoma.**—Carcinoma is a common tumor of the intestine. The usual sites of cancer are the rectum, cecum, and pelvic colon. Cancer of the small intestine is very rare. Over 60 per cent of cancers of the bowel occur in the rectum. Precancerous lesions which may be followed later by carcinoma are papilloma, adenoma, and the papillary formation occurring in chronic ulcerative colitis. By far the greatest danger is familial multiple papillomata. Precancerous lesions in the rectum are of special significance. The site of cancer of the large bowel affects its behavior and characteristics to a marked degree. Thus cancer of the colon is more common in

women, cancer of the rectum more common in men. The average duration of life without treatment is twice as long in cancer of the rectum as in cancer of the colon. Intestinal obstruction is much commoner in cancer of the descending colon and rectum than in cancer of the cecum, due to the fluid contents of the latter.

The tumor may (1) grow into the lumen of the bowel in the form of a large fungating cauliflower-like mass which soon becomes ulcerated, or (2) it may infiltrate the wall and surround the bowel as an annular growth which may cause an extreme degree of stenosis (Fig. 265). The bowel above the stenosis is dilated and hypertrophied, that below the stenosis is collapsed. Hard fecal masses may be formed on the proximal side of the stricture and these may give rise to superficial erosions of the mucosa

(stercoral ulcers). The fibrous stroma of the second form of tumor contracts, and from the outside it may look as if a tight string had been tied around the bowel (purse-string type). In this form ulceration occurs late. Mucoid degeneration may occur in the massive variety, and the large bowel is one of the common sites of the so-called colloid carcinoma.

The *microscopic appearance* is that of adenocarcinoma. The fungating type is more likely to be well differentiated than the infiltrating form, which may develop a dense stroma. The prognosis depends largely on the degree of differentiation, *i. e.*, the grade to which the tumor belongs. In cancer of the rectum Grades 1 and 2 are best treated by excision, Grade 3 and 4 by radiation.

*Spread.*—This is comparatively slow, especially in cancer of the rectum, so that the prognosis is correspondingly good. In a case of cancer of the rectum the tumor protruded from the anus, and was partially removed from time to time for seventeen years after the condition had been called inoperable, yet at autopsy there was no evidence of metastases (Wells). Growth takes place easily towards the lumen and also in the long axis of the bowel; infiltration of the muscular coat is much slower. After penetration of the muscular coat there is again spread in the long axis in the subserous tissue; the lymphatics may be distended with cancer cells and appear as opaque white beaded lines which may be mistaken at operation for tubercles. Involvement of the mesenteric and retroperitoneal lymph nodes occurs late, and so do metastases to the liver by the portal vein. I have performed an autopsy on a patient who had had cancer of the rectum over a year for which she refused operation and who finally died of pneumonia, yet neither the lymph nodes nor the liver were involved in the slightest degree. The cancer cells may penetrate the serous coat and give rise to implantation growths on the peritoneum and the surface of the pelvic organs.

**THE RELATION OF SYMPTOMS TO LESIONS.**—The early symptoms are unfortunately vague, *e.g.*, persistent constipation with occasional attacks of colicky pain which may finish as acute obstruction. A change in the habitual action of the bowels is always a danger signal. The classical text-book symptoms are late symptoms and usually indicate that the tumor is inoperable. The stools may be ribbon-like, due to malignant stricture in the infiltrating type. In the fungating type there is hemorrhage from the friable surface, and when ulceration and infection occur there are foul stools and alternating constipation and diarrhea. Blood in the stool is an early sign of cancer of the rectum, but a late sign of cancer of the sigmoid. Cancer of the cecum is often associated with severe anemia, sometimes pernicious in type, an association which it is difficult to explain.

**PAPILLOMA.**—Multiple papillomata or adenomatous polypi may occur in any part of the intestinal canal, but are most common in the large bowel, especially in the rectum. They may be very numerous, and the entire large bowel may be studded with polypi, a condition known as multiple polyposis of the intestine. The condition is often hereditary (familial). Papillomas and adenomas of the bowel must be regarded as precancerous lesions, especially in the rectum (Fig. 266). The incidence of carcinoma in a single adenomatous polyp is about 5 per cent. The structure of the papilloma is glandular, and the malignant change is into adenocarcinoma, the

line of change often being dramatically sharp (Fig. 267). Usually only one papilloma becomes malignant, but more than one may show the change. In papillomatosis there may be as many as one or two thousand, so that the chance of escaping carcinoma in such a case is infinitesimal. The

incidence of carcinoma is directly proportional to the number of papillomata.

**CARCINOID TUMOR.**—This is not an uncommon tumor of the appendix. It may occur in the small bowel, particularly at the lower end of the ileum, where it is more rare. It should be regarded as a malignant tumor usually of very low grade. In the appendix it may infiltrate all the coats, but very seldom spreads to the lymph nodes, and never kills the patient. The tumors in the intestine are more dangerous. They may be multiple, tend to produce obstruction, metastasize to the regional lymph nodes in 25 per cent of the cases, and occasionally to the liver. In the appendix the tumor usually gives rise to no symptoms, unless it causes obstruction at the prox-



FIG. 266.—Malignant papilloma of rectum.



FIG. 267.—Transition from adenoma to carcinoma.  $\times 20$ . (Boyd's Surgical Pathology.)

imal end, and it is usually discovered by accident after the appendix has been removed. The appendix itself is rarely normal, being thickened and fibrosed.

The *gross appearance* is very characteristic. Usually at the tip of the appendix a firm nodule can be felt, which on cross-section appears as a yellow ring encircling the appendix and situated in the thickened submucous coat. (Plate XII.) *Microscopically* the tumor consists of masses of spheroidal or polyhedral cells with granular or finely vacuolated cytoplasm. These cells are rich in lipoid, and it is to this that the yellow color of the tumor is due. The tumor cells are usually confined to the mucous and submucous coats, but they may reach the serous coat (Fig. 268).

It appears from the work of Pierre Masson that these tumors are *chromaffinomas* or tumors of the endocrine system, arising from the Kultschitsky cells of the intestinal mucosa which are found between the columnar cells of the crypts of Lieberkühn and belong to the chromaffin system. Both the Kultschitsky cells and the tumor cells are stained intensely by silver impregnation, so that the tumor is also called an *argentaffinoma*.

There may be a relationship between carcinoid tumors and the argentaffin-cell neuromas which Masson had previously described as occurring in obliterated appendices. These neuromas arise from the non-medullated nerve fibers in the deeper part of the mucosa. Masson has shown that the argentaffin cells may penetrate the nerves and grow along them into the mesentery. If the isolated argentaffin cells in the neuroma proliferate, a carcinoid tumor is produced.

*Carcinoma of the appendix* is very much rarer than carcinoid tumors. It is a columnar-cell carcinoma, frequently adenocarcinomatous in type, and often shows mucoid degeneration.

All other primary tumors of the bowel are rare. *Sarcoma* is more usual in the small than the large intestine. *Fibroma*, *myoma* and *lipoma* often take a polypoid form and may act as the starting point of an intussusception. *Angiomas*, sometimes multiple, have been described. *Lymphosarcoma* is not uncommon in the bowel but as it is merely part of a general lymphoid tissue neoplasia it will not be considered here.



FIG. 268.—Carcinoid of appendix. There are masses of tumor cells in the mucosa and submucosa.  $\times 150$ .

## INTESTINAL DIVERTICULA

Diverticula of the intestine usually occur in the duodenum and the lower part of the colon, but they may be met with in any part of the intestinal canal. Duodenal diverticula have already been described. The usual age period is in middle and late life. They are rare before the age of thirty

years. In the small intestine they lie in the concavity of the bowel along the line of the mesenteric attachment, as the entering vessels serve to weaken the muscular wall. In the colon they are situated on the convexity, usually in two rows between the *tænia coli*. The commonest site is the sigmoid, but they usually stop abruptly at the commencement of the rectum, because here the *tænia coli* separate out into a broad muscular sheet. Occasionally diverticula occur in the rectum.

The diverticulum is a protrusion or herniation of the mucosa and submucosa through the muscular coat at some point of weakness. Diverticula may be present in great numbers, a condition of *diverticulosis*. The usual size is that of a large pea. The opening into the lumen of the bowel may be very small or wide and gaping (Fig. 269). In the small intestine the contents are fluid, but in the colon they are fecal and sometimes in the form of concretions.

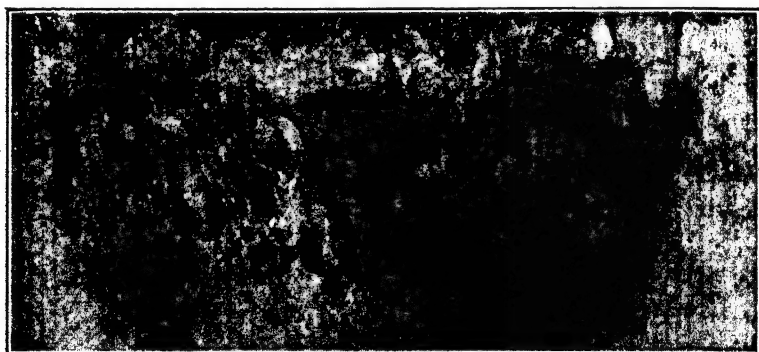


FIG. 269.—Intestinal diverticulosis, showing the openings of the diverticula on the mucosal surface.

The *cause* of the condition is uncertain. There is probably a combination of weakness of the wall and increased pressure from within. The weakness seems to be due to the loss of tone and elasticity of muscle which is characteristic of the degenerative period of life.

**Diverticulitis.**—The condition of diverticulosis is unattended by symptoms, and is often discovered accidentally by the radiologist. But if inflammation occurs in the diverticula, symptoms will be produced. This is very rare in the small intestine where the contents are fluid and readily pass out of the diverticula, but it is fairly common in the colon. Fraser remarks that “in the Century and Oxford dictionaries a diverticulum is described as a ‘way-side shelter or lodging,’ with, from the context, the underlying meaning that they are houses of ill repute where trouble is apt to brew. In the large intestine they live up to their bad reputation, and as a temporary lodging for bowel contents can give rise to endless trouble.” *Acute inflammation* often associated with the presence of a hard concretion in the diverticulum is similar to appendicitis, except that the symptoms are usually on the left side. Perforation may occur, with local abscess formation or general peritonitis.

*Chronic inflammation* is much commoner, and is accompanied by a *peridiverticulitis*. Toxins apparently leak through the mucosa and set up a chronic extramucosal inflammation, as a result of which a large amount of chronic inflammatory tissue is formed on the outside of the bowel (Fig. 270). This consists of granulation tissue which becomes converted into dense fibrous tissue. A large mass is formed which may constrict the bowel and cause stenosis, so that it is readily mistaken for carcinoma even when the abdomen is opened. The diverticula may be completely covered up by the inflammatory mass. When the excised bowel is opened it may be impossible to detect the inner openings of the diverticula, as they may be hidden by the swollen mucosa. If thin slices are cut tangential to the outer surface of the mass the blind ends of the diverticula are exposed, and a



FIG. 270.—Multiple diverticula of bowel with peridiverticular fibrosis.

probe can readily be passed through into the lumen of the bowel. On examining the gross specimen it may be difficult to decide if the condition is diverticulitis or carcinoma. A point of value is that in the former the mucosa is practically never ulcerated, while in cancer ulceration is almost always present.

**MECKEL'S DIVERTICULUM.**—In about 3 per cent of cases the vitelline duct passing from the intestine to the umbilicus fails to become obliterated. If both ends are closed but not the middle portion, the result is a cyst. As a rule only the proximal part remains open and forms a pouch-like projection from the lower part of the ileum, usually within 2 feet of the ileocecal junction. This is known as Meckel's diverticulum. It may be a mere dimple, or may constitute a fistula which opens on the umbilicus. The proximal part may remain open and be continued to the umbilicus as a fibrous cord. A loop of bowel may be forced around this cord and becomes strangulated. Sometimes the diverticulum becomes acutely inflamed, with symptoms identical with those of appendicitis. It is a common cause of intussusception in children, the diverticulum becoming turned inside out. In a certain proportion of cases (12 to 44 per cent according to different authors) islands of gastric mucosa are found in the diverticulum. These produce gastric



juice, as a result of which peptic ulcer may occur. This may cause severe hemorrhage from the bowel (especially in male children) or perforation. The dangers inherent in a Meckel's diverticulum are, therefore, three-fold, namely hemorrhage, inflammation and obstruction. Occasionally the diverticulum may contain pancreatic tissue.

**ENTEROGENOUS CYSTS.**—These are derived from diverticula of the intestine in which the communication with the bowel has been pinched off. Intestinal structures, both epithelial and muscular, can often be demonstrated in the wall of the cyst.

## HERNIA

A hernia is a protrusion of a viscus outside the cavity in which it is contained. The usual hernia is abdominal (although we speak of cerebral and other hernias), a loop of bowel, sometimes a piece of omentum, being protruded into a pouch of peritoneum which projects outward. This is an *external hernia*, and the common types are inguinal, femoral and umbilical, depending on the site of the peritoneal pouch. An *inguinal* hernia passes down the inguinal canal into the scrotum. A *femoral* hernia passes along the femoral vessels under Poupart's ligament and forms a soft swelling in the groin; it usually occurs in the female. An *umbilical* hernia appears at the umbilicus. A hernia may occur at the site of an abdominal wound owing to the scar giving way. This is a form of *ventral* hernia. The rare forms need not be mentioned. The *causes* are probably twofold: (1) local weakness, usually congenital; (2) increased pressure due to sudden muscular effort, straining at stool, etc.

In an *internal hernia* the protrusion occurs into one of the intra-abdominal pouches of the peritoneum, of which the principal are the paraduodenal pouch on the left side of the second part of the duodenum, the pouch behind the superior mesenteric artery, and the fossæ in the neighborhood of the ileocecal junction. In rare cases there may be a hernia into the foramen of Winslow and other unusual sites.

*Strangulation* of the hernia is due to an increase of pressure in the hernial sac. A fresh piece of bowel may be forced through the opening, or there may merely be an accumulation of gas and feces. The loop of bowel is forced against the sharp edge of the opening so that the venous return is interfered with. This causes further swelling of the loop, more interference with the circulation and finally complete stasis. Necrosis and gangrene rapidly develop, the wall is invaded by bacteria, and general peritonitis is the result. The clinical and pathological picture is now one of acute intestinal obstruction.

## INTUSSUSCEPTION

This is the invagination of one segment of the intestine inside another. The common site is the ileocecal junction. There is usually an exciting cause in the shape of a focus of local irritation, an adherent tuberculous or malignant gland, the presence of a polypoid tumor (adenoma, lipoma, myoma), or Meckel's diverticulum. As a result of the irritation irregular peristaltic contractions are set up, and these force the upper segment of bowel into the one below which forms a sheath. The invaginated part is forced along the bowel by peristaltic contractions and may traverse the whole length of the colon, forming a curved thick sausage-shaped mass. The contraction of the sheath prevents the escape of blood from the enclosed part, so that there is great swelling and congestion; there is hemorrhage into the bowel, and discharge of blood from the rectum is the most characteristic symptom. At first intussusception can readily be undone by traction, but the two layers

## PLATE XIII



**Acute Intestinal Obstruction Due to Volvulus**

Body opened at autopsy showing gangrenous distended coils of small intestine.

become inflamed and adhere together at the point of entry. The increasing contraction and pressure are apt to cause necrosis and gangrene of the bowel with symptoms of acute strangulation. The condition usually occurs in boys under the age of one year. It is uncommon in the adult.

Multiple *agonal intussusceptions* are often seen in the small intestine of children at autopsy. They are probably caused by irregular spasmodic contractions at the time of death. There is no inflammation nor adhesions, so that the intussusception is readily undone by traction.

## VOLVULUS

Volvulus is torsion of an organ. It is commonest in an ovarian cyst with pedicle and in the pelvic colon, but may occur elsewhere in the intestine, in the gall-bladder, spleen, testicle, and uterus with fibroids. The cause is obscure. There is probably some predisposing cause (congenital defect of attachment, etc.), and the actual twisting may be due to irregular spasmodic contraction. The vessels, first the veins and then the arteries, are occluded by the twisting of the mesentery, so that first there is intense congestion of the organ and then gangrene. (Plate XIII.) In the case of the bowel there is acute intestinal obstruction.

**ADHESIONS.**—Peritoneal adhesions are a common result of abdominal inflammation and may cause intestinal obstruction. The adhesion stretches as a fibrous band from the wall of the bowel to some fixed point, and as it contracts it causes kinking and obstruction.

## INTESTINAL OBSTRUCTION

Obstruction of the intestine or ileus may be caused in two very different ways. It may be organic or paralytic. *Organic obstruction* may be caused by carcinoma, adhesions and cicatrices, strangulated hernia, or volvulus. *Paralytic obstruction*, usually called *paralytic ileus* because the common site is the ileum, is due to inflammation of a segment of the bowel as a result of which peristaltic movements cannot pass from the segment above to the segment below, the bowels are unable to move, and the practical result is obstruction. A common cause is the pelvic peritonitis of acute appendicitis, in which a loop of ileum hangs down into a pool of pus in the pelvis and becomes completely paralyzed. Intestinal obstruction may be acute or chronic. In the acute form the blood supply to the bowel is cut off so that gangrene quickly develops; in the chronic form it is not interfered with. This difference is fundamental. The two varieties are so different that they must be considered separately.

**Acute Obstruction.**—Sudden obstruction may be caused by strangulation of a loop of bowel by a fibrous band or adhesion (strangulated hernia), twisting (volvulus), intussusception or infarction (mesenteric thrombosis or embolism). The last-named belongs to the paralytic group. Chronic obstruction due to carcinoma may suddenly become acute. The bowel below the obstruction empties and remains pale and contracted. The part above the obstruction is greatly dilated with fluid and gas and intensely congested so that it becomes deep purple in color as the veins are obstructed before the arteries. The mucous membrane undergoes necrosis, numerous small ulcers are formed, and bacteria pass through the wall of the bowel and cause general peritonitis. As the blood supply is cut off and bacterial invasion is severe, gangrene quickly develops.

The cause of the fatal toxic symptoms, most marked in high obstruction, has long been a subject of controversy. Absorption of highly toxic split-protein products from the obstruction loop may play some part (Whipple). Loss of chlorides due to the continuous vomiting have been considered of such importance that sodium chloride has been administered as a form of treatment (Haden and Orr), but without any significant impression on the high mortality. It appears probable that the most important factor is distention of the bowel, and that shock plays a leading part in severe and fatal cases. Acute experimental distention of the bowel without obstruction will produce the same symptoms as those of obstruction but without vomiting or change in the blood chlorides (Taylor). The distention is due partly to gas, partly to fluid. The gaseous distention is caused by air which has been swallowed and cannot be passed. Distention of the bowel wall is a powerful stimulant to secretion, so that great quantities of fluid are poured out. Normally from 5 to 7 liters of fluid a day enter the upper part of the small intestine to be absorbed from the lower part. In high obstruction all of this fluid is completely lost to the body, and this loss is responsible for the picture of shock, the basis of which is a marked difference between the volume of blood and the volume capacity of the vascular system. Moon points out that the post-mortem picture of acute obstruction is similar in many respects to that of shock. There is marked distention and engorgement of the capillaries in the viscera, edema and ecchymoses in the lungs and gastrointestinal mucosa, and effusions into serous cavities. Decompression of the distended bowel by means of the Miller-Abbott tube is the most valuable single method of treatment and has entirely changed the prognosis. In addition to the low blood chlorides there is a great rise in the blood urea due probably to increased tissue destruction. Large quantities of indican are excreted in the urine.

One of the most serious features of acute intestinal obstruction is loss of protein from the body. In simple obstruction without strangulation the loss is confined to plasma, so that hemoconcentration is a marked feature. When strangulation is present there is an added loss of red blood cells owing to damage to the vessels, so that the physiological disturbance is similar to that produced by massive hemorrhage.

As the distention increases, the pressure within the lumen closes the veins, the arterial blood continues to be pumped into the bowel wall, and hemorrhage occurs from the capillaries and venules. The progressive anoxia results in necrosis, gangrene, and finally rupture. These changes are greatly aggravated by the presence of feces, which may act as a secretory stimulant. In experimental obstruction if the obstructed loop is first washed out it does not become gangrenous. Even before gangrene has occurred the permeability of the distended bowel to bacteria is greatly increased, so that peritonitis is an inevitable result. Death is not due to the peritonitis but to the obstruction.

In connection with the toxemia of acute intestinal obstruction mention may be made of the experimental *autolytic peritonitis* produced by autolysis of liver tissue in the peritoneal cavity. It is a remarkable fact that when a dog's liver is removed, the animal survives longer if the whole liver is excised than if part of it is left (Mann). When one lobe of the liver is ligated, the animal dies in less than twenty-four hours, and the ligated lobe is spongy, full of gas, and contains great numbers of Gram-positive anaerobic bacilli. If a piece of liver is excised and dropped into the abdominal cavity of the same or another animal, the same thing happens, the animal dying of respiratory paralysis in less than twenty-four hours. The peritoneal cavity contains from 100 to 300 cc. of fluid exudate (peritonitis), and both the transplanted liver and the animal's own liver are swarming with anaerobes and filled with gas. The condition is called *autolytic peritonitis* because autolysis of the transplanted liver or the ligated lobe appears to cause the formation of toxic substances which increase the permeability of the bowel to *Bacillus welchii*. It is these organ-

isms which invade the liver and are responsible for the gas formation. The same result is obtained when the piece of liver is autoclaved before being transplanted, so it is evident that the bacilli are not contained in the transplant. This work illustrates the importance of the autolytic decomposition of tissue in the peritoneal cavity.

**Chronic Obstruction.**—The obstruction is slow and there is no interference with the blood supply. The usual causes are carcinoma of the bowel, especially the infiltrating variety, cicatricial contraction or adhesions, and pressure from without. Above the stricture the bowel is dilated and hypertrophied, while below it is collapsed. Hypertrophy is characteristic of slight obstruction, dilatation of severe or nearly complete obstruction, for in the latter condition the muscular coat becomes paralyzed and undergoes passive dilatation. Hard fecal masses are formed above the obstruction, and these in turn give rise to small stercoral ulcers in the mucous membrane. The irritation may cause periodic attacks of catarrhal inflammation, so that an alternation of constipation and diarrhea is highly suggestive of chronic obstruction, usually carcinomatous. Chronic malignant obstruction may at any time become acute owing to inflammatory changes at the site of the stricture with swelling of the mucous membrane.

**MECONIUM ILEUS.**—A remarkable form of ileus certain to puzzle the uninitiated occurs in the new-born. There is no narrowing of the bowel, but the lumen is blocked with thick meconium, and the wall may give way as the result of a "blow-out" following on the first feeding. In one case reported from my laboratory by Sara Meltzer the peritoneal cavity was filled with material so thick and tenacious as to suggest mucilage. In a number of cases there has been congenital stenosis of the opening of the pancreatic duct, with dilatation of the duct system and atrophy and fibrosis of the parenchyma (Kornblith and Otani). Farber (personal communication) observed this pancreatic lesion in twins, both of whom died of meconium ileus. The basis of the condition appears to be the mucosis or inspissated secretion which is the essential feature of fibrocystic disease of the pancreas (Farber).

## HIRSCHSPRUNG'S DISEASE

This is a congenital idiopathic dilatation of the colon. The pelvic colon and sometimes the entire large intestine are enormously dilated and hypertrophied. The lower part of the rectum is rarely involved. The hypertrophy is due to great thickening of the circular muscular coat, but is probably not a primary condition. Chronic inflammatory changes in the mucosa and submucosa together with stercoral ulcers are due to the great accumulation of fecal matter in the sigmoid. The bowel is evacuated at long intervals of days or weeks, when a huge quantity is passed. The abdomen is greatly distended. There are countless theories to account for this obscure condition, but it may be regarded as a form of *achalasia* or inability of the circular fibers at the junction of the sigmoid and rectum to relax. The basic lesion lies in a narrow spastic segment distal to the dilated hypertrophied colon. It is this segment which is responsible for the obstruction, and resection of this part has led to apparent cure of the condition. There is a complete absence of sympathetic ganglion cells in the affected part, together with the presence of abnormal nerve trunks at the sites of Auerbach's and Meissner's plexuses. In some cases the aganglionic segment has extended to the hepatic flexure. The physiological result is absence of peristalsis and increased tonus in the distal colonic segment.

## COELIAC DISEASE

This is a disease of young children characterized by an inability to absorb fats from the intestine. It is also known as *idiopathic steatorrhea* (outpouring of fat), *Gee's disease*, *non-tropical sprue*, and *intestinal infantilism* (marked impairment of development). It may be regarded as the infantile analogue of tropical sprue, a deficiency disease characterized by great wasting of fat, fatty stools, disturbance of calcium metabolism, and severe anemia. Coeliac disease appears to be due to a disturbance of gastro-intestinal function resulting in deficient absorption of one or more vitamins. The name, meaning relating to the abdominal cavity (*koilia*, belly), indicates the vagueness of our knowledge of the condition before recent biochemical investigation. The stools which are very bulky are loaded with fat, and are white, soft, frothy and foul-smelling due to excessive fermentation. There is a high fecal output of calcium and in consequence osteoporosis and rickets are common, together with low blood calcium and tetany. Anemia is a marked feature; it is usually of the hypochromic type, but occasionally becomes hyperchromic and macrocytic late in the disease.

**INTESTINAL LIPODYSTROPHY.**—This very rare condition was first described in 1907 by Whipple, and is therefore known as Whipple's disease. The essential lesion is a deposit of lipids, for the most part neutral fat, in the mucosa of the small intestine and the mesenteric lymph nodes. Grossly the mucosa is flecked with minute yellowish deposits, whilst microscopically the fat is contained in dilated lymph spaces of the enlarged villi and submucosa, in mononuclear phagocytes, and in occasional multinucleated giant cells. Foam cells are present in the dilated sinusoids of the mucosa and of the greatly enlarged mesenteric and retroperitoneal nodes. Clemmson noted pericardial fibrosis in 10 out of 16 cases reviewed; this was present in Whipple's first case. There is much difference of opinion as to the cause of the condition. There seems to be obstruction in the lymphatic drainage of the small bowel as well as interference with the absorption of fats, possibly due to faulty bile salt metabolism. In many of the reported cases systemic manifestations of disease outside the gastrointestinal tract antedated the local abdominal symptoms. These systemic symptoms resemble those of rheumatoid arthritis and disseminated lupus, and such lesions as arthritis, vegetative endocarditis and serositis are common. For this reason it has been suggested that Whipple's disease may be related to the rheumatic state (Peterson and Kampmeier). The chief clinical features are asthenia, anemia, arthritis, steatorrhea and abdominal distention in a middle-aged or elderly person. The disease usually proves fatal.

## MESENTERIC THROMBOSIS AND EMBOLISM

Thrombosis of the mesenteric vessels is much commoner than embolism. It may be arterial or venous. The arterial type is much more rapidly fatal and accompanied by gangrene of the bowel. Venous thrombosis is more frequent as might be expected, the veins being likely to contain intestinal toxins and bacteria. In the venous type the onset and course are slow, the result is often hemorrhagic infarction without gangrene, blood is always present in the stool, and spontaneous recovery is possible.

The result of arterial thrombosis and embolism is *infarction of the bowel*. The superior mesenteric is usually involved. When the inferior mesenteric vessels are occluded the result is less serious, because they establish communication with the superior mesenteric vessels above and the hemorrhoidal vessels below. The infarct is of the red or hemorrhagic variety, and usually occurs in the ileum or lower part of jejunum. The infarcted segment is sharply limited as a rule, thick, and

darker red in color. Gangrene may occur, particularly in arterial obstruction. The wall of the bowel is stuffed with red cells, dark blood fills the lumen, and there may be blood in the peritoneal cavity. The hemorrhage may be confined to the mucosa. Sometimes no occlusion of the vessels can be found.

The *symptoms* are extremely acute in embolism or arterial thrombosis, much less so in venous thrombosis. In the acute cases the first symptom is sudden severe *abdominal pain*, due to spasm of the bowel from sudden ischemia. *Blood in the stools* is highly significant. At first there may be diarrhea, but soon there is evidence of complete obstruction due to *paralytic ileus*. If gangrene of the bowel occurs it leads to *general peritonitis*, which rapidly proves fatal.

## HEMORRHOIDS

Hemorrhoids or piles is a condition in which the poorly supported hemorrhoidal veins become varicose and hypertrophied. *Internal* piles involve the superior hemorrhoidal veins and are covered by the mucous membrane of the rectum; *external* piles involve the inferior hemorrhoidal veins and are covered by skin. The *causes* are central and local. *Central* causes are cirrhosis of the liver (portal obstruction) and cardiac weakness. *Local* causes are constipation (causing straining at stool with dilatation of the veins), carcinoma of the rectum, and outside pressure from enlarged uterus, enlarged prostate, etc. *Every case of piles should first be examined for cancer of the rectum*, because cancer of the rectum can often be completely removed in the early stage. Some of the cases give a hereditary history.

The pile consists of a cluster of greatly dilated venules and may resemble a cavernous angioma. It is covered by mucous membrane or skin. Infection is frequent with accompanying phlebitis and thrombosis, known as an "attack of the piles." The thrombus may become fibrosed, a condition of spontaneous recovery. In rare cases the infected thrombus may become broken up and form septic emboli which are carried to the liver and there form abscesses. The tissue around the pile becomes fibrosed, and is often infiltrated with chronic inflammatory cells. Apart from the attacks of thrombophlebitis the principal symptom is repeated hemorrhage during defecation, which may lead to a marked secondary anemia.

## MELANOSIS COLI

This condition is described in Chapter 2. Granules of melanin pigment are found in the large mononuclear cells in the mucosa, but not in the epithelium. The condition is often associated with chronic intestinal stasis, especially carcinoma of the bowel. The pigmentation is usually limited by the ileocecal valve, but the appendix may be pigmented while the colon remains free. Marked pigmentation where the black color can be seen shining through the wall of the bowel is rare, but slight grades are common. The melanin is probably formed by the disintegration of proteins in intestinal stasis.

## INTESTINAL PNEUMATOSIS

This rare condition is characterized by the presence of gas in endothelial-lined spaces in the wall of the bowel and by a chronic productive inflammation. It may occur in infants or adults. In the former the cysts are mainly in the mucosa and submucosa, in the latter mainly in the serosa. Either the small or large intestine may be involved. It seems probable that the gas is derived from the intestinal lumen and enters the wall by a mechanical process through an ulceration in the mucosa (Moore). In many cases there is gross ulceration of the intestinal tract, and in others microscopic breaks in the mucosa are frequent.

## CONGENITAL ANOMALIES OF THE INTESTINES

The commonest anomaly is Meckel's diverticulum, which has already been described. Other diverticula (duodenal, intestinal) may possibly have a congenital basis, but this is doubtful as they are met with late in life. There may be *stenosis* or actual *atresia* of the bowel. The common site of atresia is the lower end of the rectum, where the condition is known as *imperforate anus*. The anus is represented by a dimple of the skin, which is separated from the lower end of the rectum sometimes by a thin membrane, sometimes by a considerable interval filled with fibrous tissue. There may be congenital obliteration of the second part of the duodenum, and much more rarely at the lower end of the ileum.

## ADDITIONAL READING

- Amoebic Dysentery.** CRAIG: J. A. M. A., 1927, 88, 19; 1934 103, 1061; Amoebiasis and Amoebic Dysentery, Baltimore, 1934.
- Antibiotic Enteritis.** DEARING AND HEILMAN: Proc. Staff Meetings Mayo Clinic, 1953, 28, 121. REINER *et al.*: Arch. Path., 1952, 54, 39. TERPLAN: Am. J. Path., 1953, 29, 595. ZAMCHECK *et al.*: Am. J. Path., 1953, 29.
- Appendicitis.** ASCHOFF: Appendicitis, Its Etiology and Pathology (English translation), London, 1932. KELLY: Appendicitis, Philadelphia, 1909. WANGENSTEEN AND BOWERS: Arch. Surg., 1937, 34, 496. WILKIE: Brit. M. J., 1931, 1, 253.
- Bacillary Dysentery.** DAVISON: Medicine, 1922, 1, 389.
- Carcinoid Tumors.** DOCKERTY AND ASHBURN: Arch. Surg., 1943, 47, 221. HUMPHREYS: Am. J. Cancer, 1934, 22, 765. MASSON: Am. J. Path., 1928, 4, 181. PORTER AND WHELAN: Am. J. Cancer, 1939, 36, 343.
- Celiac Disease.** BENNETT, *et al.*: Quart. J. Med., 1932, 1, 603. PARSONS: Lancet, 1931, 1, 61; Am. J. Dis. Child., 1932, 43, 1293.
- Diverticulosis.** EDWARDS: Diverticula and Diverticulitis of the Intestine, London, 1939. FRASER: Brit. J. Surg., 1933, 21, 183.
- Gas Cysts.** JACKSON: Surg., Gynec. & Obst., 1940, 71, 675.
- Hirschsprung's Disease.** BODIAN, *et al.*: Lancet, 1949, 1, 6; 1950 1, 19. WHITEHOUSE AND KERNOHAN: Arch. Int. Med., 1948, 82, 75.
- Intestinal Lipodystrophy.** CLEMMESON: Acta med. Scand., 1945, 121, 495. FITZGERALD AND KINNEY: Am. J. Path., 1945, 21, 1069. PETERSON AND KAMPMEIER: Am. J. Med. Sci., 1951, 221, 543. REINHART AND WILSON: Am. J. Path., 1939, 15, 483. ROSEN AND ROSEN: Am. J. Path., 1947, 23, 443. WHIPPLE: Bull. Johns Hopkins Hosp., 1907, 18, 382.
- Intestinal Pneumatosis.** MOORE: Am. J. Dis. Child., 1929, 38, 818.
- Meconium Ileus.** FARBER: Arch. Path., 1944, 37, 238. KORNBLITH AND OTANI: Am. J. Path., 1929, 5, 249. MELTZER: Canad. Med. Assn. J., 1936, 34, 186.
- Melanosis Coli.** BOEKUS, *et al.*: J. A. M. A., 1933, 101, 1. STEWART AND HICKMAN: J. Path. and Bact., 1931, 34, 61.
- Mesenteric Thrombosis.** DONALDSON AND STOUT: Am. J. Surg., 1935, 29, 208.
- Peptic Ulcer of Meckel's Diverticulum.** JOHNSTON AND RENNER: Surg., Gynec. and Obst., 1934, 59, 198.
- Radiation Lesions and Gastro-intestinal Tract.** WARREN AND FRIEDMAN: Am. J. Path., 1942, 18, 499.
- Regional Ileitis.** CROHN, *et al.*: J. A. M. A., 1932, 99, 1323. HADFIELD: Lancet, 1939, 2, 773. PEMBERTON AND BROWN: Ann. Surg., 1937, 105, 855.
- Tuberculosis.** BROWN AND SAMPSON: Intestinal Tuberculosis, Philadelphia, 1930. MEDLAR AND SASANO: Am. Rev. Tuberc., 1924, 10, 351.
- Tumors of Small Intestine.** NICKERSON AND WILLIAMS: Am. J. Path., 1937, 13, 53.
- Ulcerative Colitis.** BALL, *et al.*: Arch. Path., 1950, 50, 347. GRACE, *et al.*: Am. J. M. Sc., 1949, 217, 241. JENSEN, *et al.*: Am. J. Med. Sc., 1950, 219, 281. KIMMELSTIEL: Am. J. Path., 1952, 28, 259. PAULSON: J. A. M. A., 1933, 101, 1687. PORTIS: J. A. M. A., 1949, 139, 208. WARREN AND SOMMERS: Am. J. Path., 1949, 25, 657.
- Uremic Enteritis.** STREICHER: Arch. Int. Med., 1928, 42, 835.



## THE LIVER AND GALL-BLADDER

## THE LIVER

**DESCRIPTIVE OUTLINE.**—The description of the liver includes its size, shape, weight, color, and consistence. The *size* is very constant in health, but as the result of disease it may be much increased (tumor, amyloid) or diminished (cirrhosis). The *shape* may be distorted by disease (syphilitic scars, etc.) or by Riedel's lobe, a tongue-like process occasionally extending downward from the lower margin of the liver external to the gall-bladder. Grooves are not infrequently seen running across the upper surface of the right lobe in an antero-posterior direction; they are probably caused by folds in the diaphragm which occupy them. The *weight* is 1400 to 1600 grams in the male, 1200 to 1400 grams in the female. The *color* is a dark reddish-brown or chocolate, but the under surface is often of an indigo color due to the postmortem action of  $H_2S$  liberated from the large bowel on the iron pigment in the liver, with the production of sulphide of iron; there may be greenish staining by bile from the gall-bladder. The common pale and sometimes red patches under the capsule (pseudo-infarcts) must not be mistaken for true infarcts, which are extremely rare. The *consistence* is that of a soft solid, but the liver is friable and easily lacerated. When placed on a flat surface the dome-like curve of the upper surface becomes greatly flattened; any softening of the liver (fatty degeneration) will increase the flattening; any increase in consistence (amyloid) will prevent it.

There is one point in the microscopic appearance worthy of note. The ordinary microscopic picture of liver cells is that of cells starved or depleted of glycogen, because the sick person has eaten nothing for a number of hours before death. In sudden accidental death the cells have a foamy vacuolated appearance, in reality the normal picture of a healthy liver but apt to be mistaken by the unwary for an indication of disease; this is due to the presence of glycogen which is dissolved out by a watery fixative such as formalin (Fig. 271). Chemical estimation suggests a



FIG. 271.—Glycogen in liver cells (pale and vacuolated).  $\times 500$ .

rapid decrease in the glycogen content during the first six hours after death, but histologically there is no apparent decrease for at least ten hours (Morrione and Mamelock). The liver cell nuclei do not normally contain glycogen, but glycogen infiltration of the nuclei is quite common (Chipps and Duff). Empty-appearing or vacuolated nuclei with a peripheral arrangement of chromatin indicate a high glycogen content. Severe degrees of infiltration are infrequent, being commonest in diabetes mellitus, and occasionally present in a variety of other conditions.

Agonal changes can occur very soon after death, changes which have been mistaken for the result of disease (Popper). So-called dissociation of the liver cells which may be apparent in autopsy material is not present in biopsies taken shortly before death. In livers examined after death there is a space between the liver cells and the sinusoidal endothelium, and when this space is filled with protein-rich fluid the condition has been called serous hepatitis. This also is an agonal change and is not present during life.

### NECROSIS OF THE LIVER

In the liver the ordinary pathological conditions such as inflammation, tuberculosis and syphilis are of little importance. Necrosis of liver cells, on the other hand, is of the greatest significance. The necrosis may be divided into: (1) *diffuse necrosis*, in which all the cells in groups of lobules are affected, as in acute yellow atrophy; (2) *zonal necrosis* in which only the cells of a certain area in each lobule are affected; and (3) *focal necrosis* in which small areas of no uniform distribution are affected, as in severe bacterial infections such as streptococcal and typhoid. Zonal necrosis may be (a) *central*, this being the commonest type; (b) *mid-zone*, well seen in yellow fever; and (c) *peripheral*, as in eclampsia. From the clinical standpoint by far the most important variety is diffuse necrosis.

The characteristic reaction of liver cells to an injurious agent is necrosis. This may be called with equal truth either hepatic necrosis or hepatitis. The liver cells in comparison with other cells in the body are always living on the dangerous edge of things, for they exist in a condition of partial anoxia owing to the fact that their main source of blood is venous in origin. When the injury is slight and transient the dead cells are quickly removed and replaced by new liver cells, because no organ has greater power of reproduction. But when the injury is severe or prolonged there is likely to be a proliferation of fibroblasts resulting in fibrosis, which in the liver is known as cirrhosis. These two processes are as closely interwoven as inflammation and repair. The term hepatitis is often used for convenience to describe all stages of the process from necrosis to healing by fibrosis.

The *causes* of hepatic necrosis are many and varied. Indeed this variety of etiology is one of the chief reasons for the complexity of the subject. Our knowledge is dependent on observations on man and the experimental animal. Needless to say, we know much less about the former than the latter. At the same time it is well to remember that it is not wise to apply without reservation animal experimental observations to the human subject. On an etiological basis we can distinguish virus, toxic and deficiency hepatitis or necrosis.

**Virus Hepatitis.**—This is an acute diffuse hepatic necrosis which occurs in sporadic and epidemic form. The sporadic form is usually very mild,

and has been called in the past catarrhal jaundice. The epidemic form was extremely common among the troops of all armies in World War II. The virus is excreted in the stools. A similar form of hepatitis associated with jaundice may follow the administration of pooled supposedly normal human serum, of mumps convalescent serum, of yellow fever vaccine, and of arsphenamine (syringe contaminated by an icterogenic agent from blood of other patients). It is believed that in all these cases a virus is the causal agent. As the incubation period is around one hundred days compared with an average of thirty days in infective hepatitis it must not be assumed that an identical virus is responsible in the two groups of cases. The mortality of epidemic hepatitis is low (0.2 to 0.4 per cent), but the morbidity is high. The incubation period is remarkably long, usually a month, often longer. Jaundice is a characteristic feature and hemorrhages are frequent. The spleen is enlarged in most of the cases. Ascites was present in most of Lucké's fatal cases, due probably to low plasma proteins caused by the damage to the liver. In the brain there was acute degeneration of the ganglion cells (a characteristic virus lesion) and a mild meningo-encephalitis in 15 per cent of cases.

Viral hepatitis has a very broad spectrum as regards severity of lesions. In the most severe cases, which used to be known as acute yellow atrophy, the onset is sudden and the course very acute, with vomiting, profound jaundice, bile in the urine, diminution of liver dulness, delirium, coma and death. In civilian practice the fulminating cases are commoner in women in the latter months of pregnancy, when there may be an element of dietary deficiency due to diversion of protein to the fetus. A low nutrition level greatly aggravates the condition and there are probably other accessory factors. The prognosis is generally good, and there is complete restoration of liver function and also of structure, as shown by aspiration biopsy (Roholm and Iversen, Dible).

The *lesions* in the fulminating cases are mainly in the liver, but the kidneys are nearly always and the brain sometimes involved. The *liver*, in the fulminating cases, may lose 600 grams in weight in the course of a week. It is extremely soft, the capsule is wrinkled because of the rapid shrinkage, and the cut surface, which may resemble the spleen, presents bright yellow and darker red areas. The yellow color is due to remaining necrotic cells being stained with bile, the red represents areas in which the cells have vanished, leaving nothing but sinusoids distended with blood. Microscopically the astonishing feature is the complete disappearance of liver cells over wide areas. This is not evident in aspiration biopsies made shortly before death, and may therefore be regarded as largely due to post-mortem autolysis. The remaining cells are necrotic and disintegrating (Fig. 273). Inflammatory cells, often polymorphonuclears, are seen in the portal areas, and there may be endophlebitis of the portal veins. An important feature is preservation of the reticulin outlining the columns of liver cells (Fig. 272). In those cases which recover (the vast majority) repeated aspiration biopsies show regenerating liver cells growing along this framework to form new columns. If no regeneration occurs the sinusoids collapse, the reticular fibers become fused together to form collagen, and cirrhosis may result.

*Subacute necrosis with nodular hyperplasia* is the name applied to those cases of massive necrosis which recover from one or more attacks. The patient frequently has had a number of recurring attacks of jaundice, epigastric pain, vomiting and fever. The liver is coarsely nodular and scarred, the nodules of regenerated liver tissue being often quite large. This is healed yellow atrophy or post-necrotic cirrhosis.

In the *kidneys* acute tubular degeneration (nephrosis) is the rule. Whether this is a primary effect or is secondary to liver damage is not certain. The presence of leucine and tyrosine in the urine, protein cleavage products of necrotic liver cells, is in favor of the second view. In the *brain* there was acute degeneration of the ganglion cells in 15 per cent of

Lucké's 125 fatal cases, giving a clinical picture of encephalitis. This is a typical viral type of lesion, suggesting that it is probably not secondary to liver damage.

**Toxic Hepatitis.**—Necrosis of the liver may be caused by drugs (arsphenamine, chloroform, cinchophen), by poisons used for suicidal or homicidal purposes (phosphorus, mercury), and by substances used in technical and manufacturing processes (carbon tetrachloride, tetrachlorethane and trinitrotoluene). The action of these substances can be observed both in man and in experimental animals. The effect depends both on the size of dose and on the length of the time that the poison acts (Cameron and Karunaratne, Himsworth and Glynn). When rats are given a single dose, illness develops in a few hours, reaches its height in twenty-four hours, and

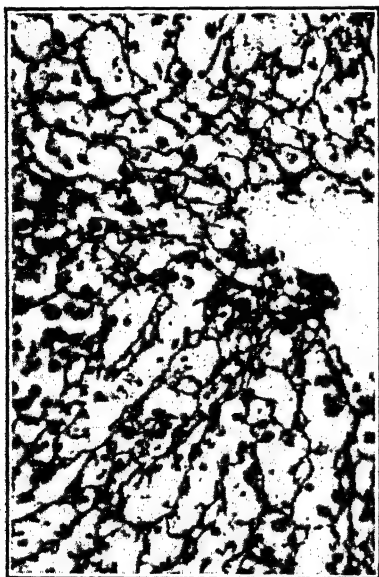


FIG. 272.—Preservation of reticulum around central vein in hepatic necrosis.

is followed by complete recovery by the end of two weeks. The necrosis is zonal in type, central or peripheral depending on the poison, with restoration to normal in the course of a fortnight. When large doses are given at short intervals the necrosis is more massive and may be followed by cirrhosis.

**Deficiency Hepatitis.**—Knowledge of this form is due to feeding experiments on laboratory animals. Relatively little is known about the condition in man. Lack of lipotropic factors in the diet, especially choline and the sulphur-containing amino acids, methionine and cystine, result in an extreme degree of fatty infiltration of the liver followed by necrosis. Prolonged administration of a low-protein diet deficient in these essential amino acids also results in necrosis. These varied substances together with

the B vitamins serve to protect the liver against the poisons mentioned above and also against virus infection. This is the basis of the high protein-low fat diet reinforced with B vitamins and sulphur-containing amino acids in infectious and toxic hepatitis. In chronic alcoholism the diet is nearly always grossly deficient in the protective food substances. This is also true of races, such as the African Bantu, in whom cirrhosis (and carcinoma) of the liver is particularly prevalent. It is possible that in man toxic or viral attacks and deficiency in protective elements may be combined, particularly in the severe cases.

The beautiful experimental observations of Hartroft on the changes produced by a choline-deficient diet on the liver of the rat are highly suggestive in relation to human cirrhosis. The first change was an accumulation of fat in the cells farthest from the portal canals. The size of these fat spaces became ever larger, until they measured up to 100 microns in diameter, or 7 times the normal. No single cell could be distended to this extent. It was found that these fat spaces represented many cells which had become fused owing to rupture of their overstretched walls. In some cases as many as 80 nuclei could be seen in serial sections, so that the structure represented that number of liver cells. This fat unit Hartroft has named fat cyst. In the course of time the fat disappears, leaving the liver via the hepatic veins and bile ducts, the fat cysts atrophy, and at the same time become surrounded by fine fibrils of connective tissue which can be traced to the adventitial sheaths of nearby central veins. Identification of central and hepatic veins was facilitated by the injection of India ink into the respective veins. Cysts which have ruptured into bile canaliculi take on the appearance of atypical bile ducts lined by dedifferentiated hepatic cells, but their true nature at once becomes apparent in frozen sections stained for fat. This is the explanation of the apparent proliferation of bile ducts which is a striking feature of human cirrhosis. The fibrous tissue in the trabeculae represents consolidated, not proliferated, reticular stroma. Only a relatively small fraction of the components of "fibrous" trabeculae gives the characteristic reaction for collagen with connective tissue stains. The bulk of the trabeculae consists of remnants of fat cysts, interlacing channels lined by simple epithelium ("new bile ducts"), and aggregates of ceroid in atrophic cysts. It is small wonder that the fibrosis may appear extreme when it is recalled that a single fat cyst may represent as many as eighty hepatic cells which ultimately disappear. An abnormal accumulation of fat in the liver cells is therefore the basic lesion responsible for the cirrhosis. The fibrous trabeculae around the central veins spread along the pathway to neighboring central veins, a pathway which runs midway between the nearest portal areas. Liver lobules are often arranged in petal form around main branches of the portal vein. Thus centrilobular areas lie close to the main portal canals at many points. The mimicry of bile ducts by the atrophic fat spaces in paraffin sections adds to the illusion of a portal distribution. The resulting cirrhosis, while not central in the sense of the centrilobular fibrosis of cardiac cirrhosis, is at least non-portal.

An additional feature of great interest observed by Hartroft in his experimental animals was the presence of fat emboli in the lung, kidney, and heart. The fat entered the pulmonary alveoli and was taken up by phago-

cytes. Hartroft found fat cysts to be an invariable accompaniment of alcoholic cirrhosis in man, and these cysts were larger than those of the rat. It seems reasonable to suggest that this fatty disintegration of liver cells is an important factor in the pathogenesis of many cases of human cirrhosis. The possibility that fat may be transported from the liver to other organs causing embolism with corresponding after-effects certainly provides food for thought.



FIG. 273.—Acute diffuse hepatitis. There is an extreme degree of destruction of the liver cells.  $\times 350$ .

Popper and Franklin have made a valuable comparison between cases of hepatic necrosis in military personnel and those in a large civilian hospital. They find that the great majority of the military cases present lesions similar to those of known cases of virus hepatitis as described by Lucké, whereas the lesions of most of the civilian cases resembled those of cases known to be caused by such toxins as carbon tetrachloride. The authors have accordingly named these two groups provisionally as viral and toxic. It is admittedly impossible to determine in most cases the exact nature of the etiological agent, and a number of cases refuse to fit into either group. As the death rate from the toxic form is the higher it is natural that more of these should be seen in the autopsy room. It may well be that in the nonfatal cases the viral outnumber the toxic.

In the *viral group* there seems to be a rapid, almost explosive disintegration of liver cells, small fragments hardly recognizable as cellular in nature being produced. The entire lobule is involved. Cords of regenerating liver cells which may resemble bile ducts are seen at the periphery of the lobules in the later stages. There is a marked mesenchymal cellular reaction with phagocytosis of the particles of cells.

In the *toxic group* there is gradual cell death rather than rapid disintegration, the nuclei disappear, and large anuclear cellular remnants (ghost cells) are seen, especially in the central zone. There is fatty degeneration and coagulation necrosis, including Mallory's "alcoholic hyaline" change. The distribution of the lesions is

zonal, with frequent involvement of the center of the lobule. There is little regeneration of the liver cells and a minimum of inflammatory reaction. Both acute viral infections and poisons can produce severe hepatic necrosis, but in the viral form there is a well marked cellular infiltration and preservation of reticulum as shown by silver staining.

**ECLAMPSIA.**—In this grave complication of the later stages of pregnancy there is a hemorrhagic necrosis, usually peripheral in distribution, in about half the cases (Fig. 274). There may be large red splashes on the surface of the liver, so that the organ presents a striking and highly characteristic picture. The red lesions are due to fibrinous thrombosis in the portal vessels and the adjacent sinusoids, with accompanying escape of blood into the parenchyma. It used to be thought that the liver lesions were the essential feature of eclampsia, but it is now believed that the basic changes are in the kidney.

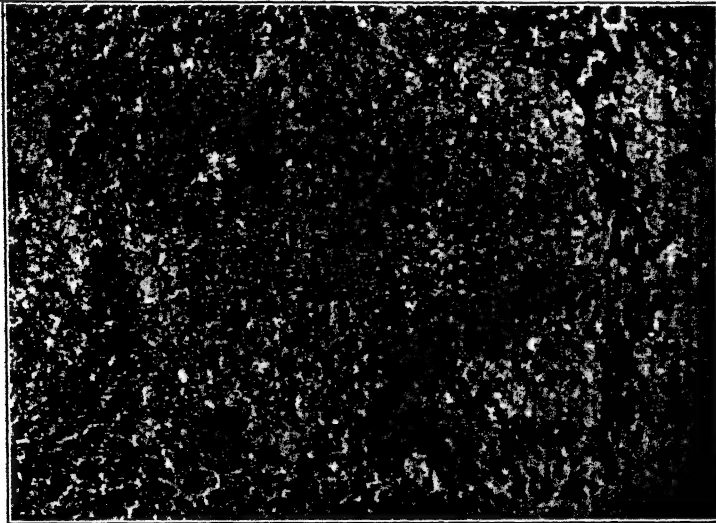


FIG. 274.—Liver in eclampsia, showing peripheral hemorrhagic necrosis.

## CIRRHOSIS OF THE LIVER

Cirrhosis of the liver has been defined by Moon as a progressive chronic inflammation, diffuse in extent, accompanied by fibrosis, retrogressive changes in the parenchymal cells and proliferation of remaining cells in the direction of regeneration. The word is derived from the Greek *kirros*, meaning tawny, and was used by Laennec to describe the color of the liver. The connotation of the word has now completely changed.

A satisfactory classification of cirrhosis is impossible, because the antecedents of the condition are unknown in the great majority of cases. Two main forms can be recognized, portal cirrhosis and biliary cirrhosis, and two lesser forms of minor importance, pigment cirrhosis or hemochromatosis and syphilitic cirrhosis.

**Portal Cirrhosis.**—This is the common form of cirrhosis. The essence of the condition is destruction of the hepatic cells and their replacement by

fibrous tissue. It is probable that the fibrous tissue is stimulated to proliferate by the injurious agent.

**ETIOLOGY.**—There is no one cause of portal cirrhosis, just as there is no one cause of contracted kidney. Any agent which leads to diffuse necrosis of hepatic cells can give rise to cirrhosis. The known causes of liver necrosis have already been enumerated. Some of these, such as the use of cinchophen in proprietary medicines, can produce typical portal cirrhosis. In the great majority of cases of cirrhosis no cause can be demonstrated.

It seems justifiable to distinguish two main groups of human portal cirrhosis. (1) A common primary or idiopathic type due to a variety of slow-acting agents. This is the form described long ago by Laennec, and is known as Laennec's cirrhosis. (2) A more unusual type secondary to one or more attacks of acute or subacute hepatic necrosis. This may therefore be called post-necrotic cirrhosis; it is the multiple nodular hyperplasia of Marchand. The former type is more common in men, the latter is much commoner in women.

1. In the great majority of cases cirrhosis is the result of a slow long-continued necrosis, a nibbling away of hepatic cells and their replacement by fibrous tissue. The cause of this gradual destruction is uncertain. There is no history of attacks of any kind. Anything which interferes with tissue respiration (oxidation) in the hepatic cells may give rise to necrosis and finally cirrhosis. When there is anoxia of the hepatic cells, efficient carbohydrate metabolism cannot take place, and the cells become infiltrated with fat which replaces the normal glycogen. Marked fatty infiltration appears to be an antecedent of cirrhosis in many cases, especially when alcohol is a factor (Connor). Many of the hepatic poisons, such as chloroform, ether, carbon tetrachloride, and alcohol, interfere with cell respiration in the liver, and this is followed by glycogen depletion, accumulation of fat, and eventual disintegration of the liver cells. The action of these and other agents is intensified by infection, pregnancy, and dietary deficiencies. In chronic alcoholism there is a low intake of protein, carbohydrate and vitamins, diminished storage of glycogen, and fatty replacement of the liver cells. These conditions render the liver more vulnerable, with consequent necrosis and cirrhosis. There seems to be no doubt that alcohol can cause portal cirrhosis. The difficulty is to know how frequent a cause it is. The pathologist must not be misled by a negative history of alcoholism in these cases, for chronic alcoholics are notorious liars in respect to their drinking habits.

2. The post-necrotic type may be due to agents known to cause diffuse necrosis (cinchophen, arsphenamine, trinitrotoluene) or may be the sequel of viral (acute infectious) hepatitis. This is the "toxic cirrhosis" of Mallory. There may be repeated attacks of jaundice with epigastric pain, vomiting and fever, attacks which are designated by the clinician as hepatitis. At each attack large groups of liver cells are destroyed. If the patient survives, these areas are replaced by fibrous tissue, whilst the remaining cells undergo compensatory nodular hyperplasia. As the result of the hyperplasia quite large nodules of new liver tissue may be formed.

In actual practice it is often difficult or impossible for the pathologist to differentiate between the two types of cirrhosis, although the clinical



history is usually of value. Indeed it is possible that the distinction itself may be unjustifiable, and that final simplification may be reached by the statement that hepatic cirrhosis is merely the end stage of hepatitis, its character depending on the type of injurious agent, its dose, and the time during which it operates.

*Experimental hepatic injury* has been produced in laboratory animals in a variety of ways. (1) Cirrhosis may follow the abnormal accumulation of liver fat which occurs in the rat when fed a diet deficient in the ordinary lipotropic factors, choline or its precursors betaine and methionine. In the early stages, this type of cirrhosis is of the so-called monolobular variety, but in the late stages the nodularity may be coarse and irregular. (2) A *relative* deficiency of lipotropic factors may be induced by increasing other major components unduly, as in high-fat diets and high-carbohydrate diets



FIG. 275.—Portal cirrhosis of the liver. The external surface has a coarsely granular hob-nail appearance.

where the increase in these portions has been achieved at the expense of the lipotropic-containing protein fraction. Similarly, excessive consumption of alcohol may induce a relative lipotropic deficiency, leading to the so-called alcoholic cirrhosis. (3) Another type of nodular cirrhosis has been produced experimentally in a variety of animals by the administration for several months of toxic agents, such as the azo dye known as butter yellow (paradimethylaminoazobenzene), chloroform, carbon tetrachloride, other chlorinated organic compounds and certain inorganic substances (phosphorus, selenium, etc.). The new connective tissue is absorbed in part or completely some months after the rats are restored to a normal diet (Steinbert and Martin) (4) Another type of liver lesion, *massive hepatic necrosis* (Himsworth), has been produced by protein deficiency which results in an inadequate intake of the sulfur-containing amino acids methionine and cystine, provided there is a concomitant deficiency of vitamin E. There is recent evidence that to produce necrosis, these diets must contain at least a small amount of fat and it has been found that many American yeasts

contain a protective factor (Schwartz's Factor 3) which will prevent the development of massive hepatic necrosis even when the diet contains fat and is deficient in methionine, cystine and vitamin E.

**LESIONS.**—The *liver* is atrophic in the later stages, but in the earlier stages it may be larger than normal. This is especially the case when the fatty changes due to chronic alcoholism are marked. In extreme cases it is only one-half the normal weight.

The consistence is very firm owing to the large amount of fibrous tissue and it is usually difficult to cut. The surface of the liver has a characteristic nodular appearance (hob-nail liver), and the cut surface is correspondingly nodular (Fig. 275). The nodules vary much in size. Large nodules over 2 cm. in diameter suggest the post-necrotic type cirrhosis, and these may be so large as to produce distortion of the liver. In ordinary cirrhosis the nodules are small (hob-nail liver) and the surface may be merely granular. The color varies. The islands of liver tissue may show no change from the normal; they may be yellow from fatty changes, or green due to staining with bile. There is often a general brownish or tawny coloration (to which the name of cirrhosis was originally due) caused by the deposition of iron pigment.



FIG. 276.—"Alcoholic hyaline" in degenerating liver cells.  $\times 450$ .

*Microscopically* the earliest change is a proliferation of the connective tissue in the portal space. Normally there is sharp delineation of this space, but in cirrhosis the boundary is broken by proliferation of fibroblasts between the degenerated peripheral cells. As the disease advances groups of liver cells of very varying size are separated by broad strands of fibrous tissue. The islands of liver cells may resemble lobules, but this appearance is fictitious; there is no true lobular arrangement, for there is no central vein in the center of the islands, which for the most part represent new formations due to regenerative hyperplasia. The portal vein does not drain into the new nodules, which get their blood supply from the hepatic artery. The salient feature is thus loss of hepatic architecture. The nodules are composed largely of new cells which show irregularity of size and arrangement. Between the nodules the liver cells have disappeared. Occasionally some of the degenerating cells contain a peculiar hyaline material staining deeply with eosin (Fig. 276); this appearance used to be considered as characteristic of alcoholic cirrhosis (Mallory), but this view has had to be abandoned. The connective tissue forms broad bands between the islands of liver cells, and may be young and cellular or old and fibrous. Chronic

inflammatory cells are present, sometimes in large numbers, but the chief feature is the greatly increased number of bile ducts. Cords of young liver cells may simulate new bile ducts. There is evidently a proliferation of biliary epithelium which establishes connection with the new groups of liver cells. Jaundice only appears late in the disease; even then it is seldom marked.

Testicular atrophy is a common finding in hepatic cirrhosis. It is much more frequent in those below the age of fifty years than in those above that age. It has been suggested from experimental evidence that there is failure of normal inactivation of estrogens by the liver, and that this results in atrophy of the testes (Morrione). The urine from patients with cirrhosis



FIG. 277.—Portal cirrhosis of liver. Great replacement of liver cells by fibrous tissue, with formation of new bile ducts.  $\times 50$ .

of the liver contains increased amounts of free estrogens, and it is well known that administration of estrogens leads to testicular atrophy. Hyperplasia of the breasts in the male (gynecomastia) and metaplasia of the epithelium of the glands and ducts of the prostate also occurs, though less frequently (Bennett *et al.*).

**BILIARY CIRRHOSIS.**—This term indicates that the cause of the cirrhosis is to be found in obstruction in the biliary system. The obstruction is usually extrahepatic, and is then known as secondary. When intrahepatic and largely hypothetical it is called primary. Biliary cirrhosis is much less common than portal cirrhosis.

The chief causes of *secondary biliary obstruction* are cancer of the head of the pancreas, stone in the common bile duct, and benign stricture of the duct. Cancer of the head of the pancreas is likely to cause rapid dilatation

of the hepatic ducts rather than cirrhosis, which is a slow process. Congenital obstruction of the bile passages in children leads to the obstructive type of cirrhosis.

The *liver* is usually of normal size, but it may be enlarged. The surface is smooth or very finely granular and the whole liver may be stained an intense green. The bile ducts are dilated and tortuous and new ducts appear to be formed. The connective tissue in the portal areas is increased and infiltrated with chronic inflammatory cells. Although sometimes the connective tissue encircles individual lobules (Fig. 278), in most cases the distribution cannot be distinguished from that of portal cirrhosis. The bile canaliculi in the interior of the liver cells are distended with thick bile to such an extent that the liver cells may be disintegrated (Fig. 279); they



FIG. 278.—Biliary cirrhosis. The cirrhosis is monolobular in type. Numerous bile ducts in connective tissue.  $\times 50$ .



FIG. 279.—The effect of biliary obstruction. The bile canaliculi are distended with bile and the liver cells are disintegrating.  $\times 600$ .

seem to burst, the canaliculi are ruptured, and the inspissated bile is seen between the liver cells and the walls of the sinusoids. There is marked jaundice but no ascites. The spleen may be enlarged.

*Primary biliary cirrhosis* is synonymous with *Hanot's cirrhosis*, a rare condition characterized by less extreme jaundice, a very large smooth green liver, and an unduly large spleen. It is supposed to be due to intrahepatic biliary obstruction, possibly the result of antecedent hepatitis, but there is no pathological evidence to support this view.

**HEMOCHROMATOSIS.**—This rare condition, known also as bronzed diabetes, is not really a disease of the liver but a disturbance of iron metabolism. The liver

contains enormous quantities of iron in the form of hemosiderin. The pigment is present in the liver cells, Kupffer cells and connective tissue. Owing to the continued irritation of the pigment the liver cells become necrosed and disappear, and there is a marked proliferation of connective tissue with a resulting *pigment cirrhosis*, the microscopic appearance of which is identical with portal cirrhosis. The liver is usually enlarged and of a characteristic brown color. Carcinoma of the liver is a complication in about one-fifth of the cases. The general question of hemochromatosis is discussed in Chapter 2.



FIG. 280.—Esophageal varicosities which caused severe hematemesis.

**HEPATOLENTICULAR DEGENERATION.**—This rare condition, known as Wilson's disease, is the most puzzling of all the forms of cirrhosis. As the name implies, there are lesions of the liver and lenticular nucleus of the brain. The hepatic lesion is a cirrhosis indistinguishable from Laennec's cirrhosis. The relation of this to the cerebral lesion is uncertain, and is discussed in Chapter 31.

**THE RELATION OF SYMPTOMS TO LESIONS.**—Although the cirrhotic liver may show marked disorganization and actual destruction of the parenchyma of the organ, there is a remarkable freedom from symptoms of hepatic insufficiency, owing to the great margin of safety which the liver possesses. The symptoms are mainly those of obstruction, both portal and biliary.

*Portal Obstruction.*—This is the chief effect of portal cirrhosis. There is congestion of the entire portal circulation with digestive disturbances, anorexia, etc. Ascites develops owing to transudation through the walls of the mesenteric veins. The spleen is enlarged. It differs from the cardiac spleen of heart disease in being much larger but not nearly so hard. In the cardiac spleen the sinusoids are distended with blood, while in the cirrhotic spleen there is a cellular increase of the pulp and marked deposits of hemosiderin. The splenic enlargement of cirrhosis is not always due to portal congestion, for it may be present in biliary cirrhosis. It is probable that the infective or toxic agent which acts on the liver acts also on the spleen. This is apparently the case in Banti's disease.

A *collateral circulation* is established with the systemic circulation, but this seldom proves sufficient. Moreover *varicose dilatations* are apt to develop at the points where the two circulations communicate. Three of these are of clinical importance. (1) At the lower end of the esophagus and the cardiac end of the stomach the varicosities may give way, causing severe or fatal hemorrhage (hematemesis) (Fig. 280). The injudicious use of the stomach tube may cause rupture of these veins. They are easily overlooked at autopsy because the veins collapse when the liver is removed, so that the esophagus should be examined first in a case of cirrhosis. (2) Less frequently varicosities (hemorrhoids) are formed at the junction of the inferior mesenteric and hemorrhoidal veins. (3) The epigastric veins of the abdominal wall which communicate with the veins at the hilus of the liver by way of the round ligament become dilated, and there may be a ring of varicosities around the umbilicus known as the *caput medusæ*. Injection methods show that innumerable anastomoses develop between the portal and hepatic veins.

The cause of the venous obstruction is not stenosis due to the contracting fibrous tissue as is commonly supposed, although it cannot be denied that this may play some part. The hepatic-portal vein anastomoses may serve to raise the pressure in the portal system. Injection and corrosion preparations show that there is a great diminution of the total vascular bed, so that the main trunks of the portal vein are stenosed and the finer radicles disappear. The reason for this appears to be the great destruction of the liver parenchyma which is the essential lesion in cirrhosis, followed by gradual obliteration of the now functionless radicles. It is true that new groups of liver cells are formed, but these are not true lobules, and it can be seen from injection preparations that they are completely devoid of venous channels.

There may be marked *hypoproteinemia* in portal cirrhosis. This causes a low serum colloid osmotic pressure, which probably accounts for the edema which may develop, and partly at least for the ascites.

*Biliary Obstruction.*—Jaundice is the great symptom of obstructive biliary cirrhosis, the bile being unable to escape from the bile ducts and accumulating in the blood. Cases of portal cirrhosis often develop jaundice in the terminal stages, but it is seldom severe. It may be explained by the extreme disorganization and distortion of the normal architecture of the liver. Indeed it is to be wondered at that jaundice is not a more marked feature of portal cirrhosis.

## ABSCESS OF THE LIVER

An abscess may be caused by infection reaching the liver by way of (1) the hepatic artery, (2) the portal vein or (3) the bile duct.

(1) *Hepatic artery infection* is a manifestation of pyemia. Large numbers of small, even microscopic, abscesses are scattered through the liver. The condition is a terminal one, and death occurs before the abscesses have time to attain any size.

(2) *Portal vein infection* is usually due to septic embolism from a focus of suppuration in the appendix, or sometimes in the stomach or intestine. It is a portal pyemia, so that the abscesses are multiple, being most numerous in the right lobe. Occasionally there is direct extension of the inflammation from the septic focus in the gastro-intestinal tract along the portal vein to the liver, a condition of suppurative, *pylephlebitis* (*pyle*, a gate). The portal vein is filled with a soft infected thrombus, and when it is slit open it can be followed down to the original source of the infection.

*Amœbic abscess* or tropical abscess is a special example of portal vein infection. It is a common complication of amœbic dysentery, the amœbæ being carried from the intestine to the liver by the portal circulation. The abscess may be single or multiple. The common site of the solitary abscess, which may attain a great size, is the upper part of the right lobe causing upward displacement of the right dome of the diaphragm. The contents are viscid and chocolate-colored, but are necrotic rather than purulent unless secondary infection occurs. It may rupture into the peritoneum or lung. The condition is often a very chronic one.

(3) *Bile-duct infection* causes cholangitic abscesses. They are associated with calculus obstruction in the ducts or suppuration of the gall-bladder. The abscesses are multiple and of considerable size, and the bile ducts are filled with pus.

### SYPHILIS OF THE LIVER

Syphilis of the liver used to be a subject of importance. Now it has sunk to the obscurity of small type. It may occur in two forms, congenital and acquired. The congenital lesions are usually diffuse, the acquired are localized.

**CONGENITAL.**—This form occurs in a child the subject of congenital syphilis. In the early stages the liver is enlarged; later it may be contracted. In Levaditi preparations the liver is found to be swarming with spirochetes, which are distributed diffusely through the entire organ. This serves to explain the lesion which is known as *syphilitic cirrhosis*, and takes the form of a fine diffuse fibrosis which penetrates the lobules and may separate the liver cells (Fig. 281).

**ACQUIRED.**—The lesion of the acquired form is the tertiary gumma of which there may be several (Fig. 283). They may be of considerable size. The left lobe tends to be more involved than the right. There may be tumor-like masses on the surface. As the gummata heal abundant scar tissue is formed, and when this contracts deep fissures are produced. These fissures divide the liver into irregular lobes, so that sometimes a remarkable degree of deformity is produced which is absolutely characteristic of the condition. Such a deformed and scarred liver is called *hepar lobatum* (Fig. 282).

### TUBERCULOSIS OF THE LIVER

This may take two forms. (1) *Miliary tubercles* are scattered through the liver in general miliary tuberculosis. They are usually found in the region of the portal tract. (2) The solitary tubercle or *tuberculoma* is a rare condition in which a large caseous mass is formed which is easily mistaken for a gumma. Indeed the differentiation may not be possible unless the tissue is stained for tubercle bacilli.

### ACTINOMYCOSIS OF THE LIVER

The infection usually spreads from a primary focus in the cecum or appendix. Secondary abscesses are formed in the liver. These at first are arranged in small



FIG. 281.—Syphilitic cirrhosis. The individual liver cells are separated by fine connective tissue.  $\times 400$ .

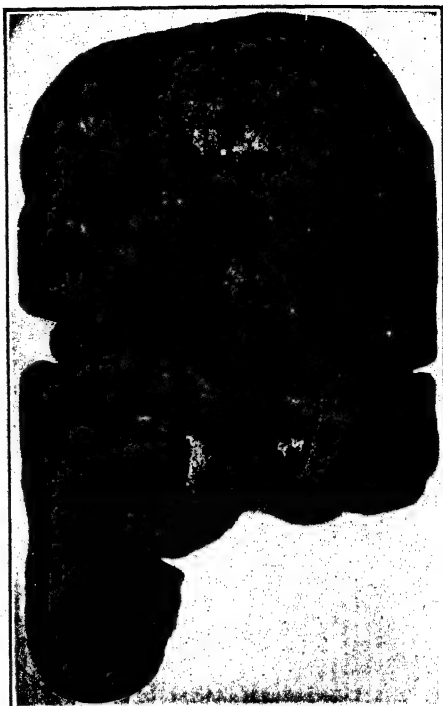


FIG. 282.—Hepar lobatum.



FIG. 283.—Gumma of liver.



groups so that the affected area has a loculated or honeycomb appearance which is very characteristic. In some cases it resembles a sponge full of pus. Later large abscesses are formed containing the familiar sulphur granules in which the mycelia can be demonstrated.

## TUMORS OF THE LIVER

Although the liver has such remarkable powers of hyperplasia, primary tumors both innocent and malignant are quite rare. Secondary tumors are very common, because all the blood from the gastro-intestinal canal and pancreas passes through the liver, and it is supplied in addition by the hepatic artery.

**Primary Carcinoma.**—Primary cancer is as rare as secondary cancer is common. Before diagnosing a tumor as primary carcinoma, every other possible source of growth must be excluded. There are two forms of primary carcinoma of the liver: (1) *hepatoma* or liver-cell carcinoma; this is the usual variety; (2) *cholangioma* or bile-duct carcinoma. In typical cases the differentiation is very easy, but in atypical cases it is very difficult.

**HEPATOMA.**—There may be one large tumor with a few small outlying nodules, or more rarely multiple small nodules are scattered throughout the liver without any large primary growth. The massive tumors are soft, necrotic, and often show hemorrhage. When the growths are multiple there has usually been spread through the liver by portal vein, for invasion of the vein is common. In some cases it appears probable that the tumors are of multicentric origin. This is especially so with the small multiple type of growth. The intervening portions of the liver may be very firm owing to portal cirrhosis which is commonly associated with primary carcinoma, and may give the liver a finely nodular appearance. *Microscopically* the tumor consists of liver cells very irregular in size and arrangement. They are arranged in interlacing strands, but sometimes show an attempted alveolar or even adenomatous formation which is easily confused with that of bile-duct carcinoma. Multinucleated giant cells may form a striking feature; indeed some of the largest carcinomatous cells occur in this tumor (Fig. 284). Cirrhosis is often prominent in the remaining parts of the liver; it is of the portal type. It is probable that the cirrhosis is primary, and that the tumor arises from the associated hyperplastic nodules. Carcinoma occurs as a complication of hemochromatosis in some 20 per cent of cases of that disease.

Primary cancer of the liver has a curious geographic distribution. It is very rare in Europe and America, but it is very common in the natives of the Far East, especially some parts of China and Malaya, and of South Africa. Indeed in Java and other large centers it is the commonest of all forms of carcinoma. Experimental carcinogenesis suggests a probable explanation of the mystery. Investigators in Japan induced primary cancer of the liver in mice and rats by adding certain azo dyes, such as butter yellow, to the diet (Sasaki and Yoshida). European and American workers failed to confirm these results. The reason for this was found to lie in the diet. The Japanese animals were fed on rice and carrots, whereas the European and American animals were fed largely on wheaten cereals.

When the latter animals were fed on the Japanese diet, the butter yellow produced cancer of the liver. It was then found that the protective factors in the diet were casein and riboflavin (Sugiura and Rhoads). It may be noted that when rats are kept for a long period on a choline-deficient diet a considerable proportion of them develop carcinoma of the liver, either hepatoma or adenocarcinoma (Copeland and Salmon). It is highly probable that the explanation of the peculiar geographic incidence of human liver cancer is a matter of diet.



FIG. 284.—Hepatoma. The very large cells are characteristic of this tumor.  $\times 200$ .

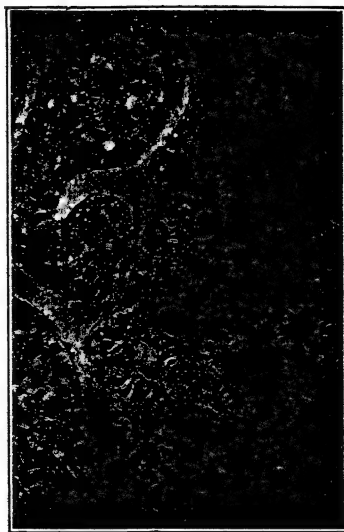


FIG. 285.—Cholangioma. The tumor cells in places are arranged around ducts.

**CHOLANGIOMA.**—Bile-duct carcinoma is less common than hepatoma and less often associated with cirrhosis. The tumors are multiple, and the liver is enlarged and stained with bile. The *microscopic appearance* is that of an adenocarcinoma in typical cases, the lining cells resembling those of the bile ducts (Fig. 285). Giant cells are seldom seen. In the more atypical forms the structure resembles that of a hepatoma.

**SYMPTOMS.**—The symptoms of primary carcinoma of the liver are often due as much to the cirrhosis as to the tumor. Jaundice and ascites are common. A very rapidly recurring ascites suggests malignant invasion of the portal vein. Fever is present in over 10 per cent of cases. It may be compared with the fever of gumma of the liver, and in both cases seems to depend on a mass of necrotic material in the liver.

**Secondary Carcinoma.**—Secondary carcinoma of the liver is very common. The spread may be: (1) from the gastro-intestinal tract by way of the portal vein, (2) by the systemic circulation (hepatic artery), (3) by the lymphatics, (4) by direct spread from the gall-bladder, stomach, or pancreas. Cancer of the stomach is the most common primary site, but cancer of the breast and the lung deserve special mention. Other sites are the kidney, adrenal, uterus, and eye (malignant melanoma).

The liver may be enormously enlarged or of normal size. The tumors are multiple and are more on the surface than central in position. They vary greatly in size, are soft and necrotic, and may be yellow from necrosis, green from bile-staining, or red from hemorrhage. The superficial tumors show a falling-in of the center due to necrosis, which from the outside gives an appearance of dimpling known as *umbilication*. There is no cirrhosis.

Willis points out that invasion of the larger portal tributaries in the liver by tumor growth is responsible for the multiplicity of nodules. There may be only one metastasis in the first place, but this mechanism, which can be demonstrated by cutting the liver into thin slices, is responsible for the multiplicity. Invasion of efferent veins is an important factor in further dissemination to the lungs.

**SARCOMA.**—Primary sarcoma is extremely rare. Secondary sarcoma is not common.

**INNOCENT TUMORS.**—An *adenoma* is very rare. It usually remains small and is composed of irregular columns of liver cells; the normal architecture of the lobule is lost. The nodules in a cirrhotic liver when large may be mistaken for adenomata. A *solitary hyperplastic nodule* in an apparently normal liver may be several inches in diameter and press on the surrounding organs. It is not encapsulated like a true adenoma, but can be removed surgically. *Cavernous hemangioma* is fairly common. It is found by accident at autopsy and causes no symptoms. It forms a small red or purple area always situated on the surface and apt to be mistaken for an infarct. It consists of cavernous blood-filled spaces.

## PARASITES IN THE LIVER

**Hydatid Disease.**—The presence of hydatid cysts in the liver causes a tumor-like enlargement. It is a comparatively rare disease except in those sheep-raising countries where men come into intimate contact with dogs, *e.g.*, Australia, South America, etc. In these countries it is very common. The life cycle of *Tænia echinococcus*, of which the cystic stage is the hydatid, has already been traced in Chapter 8. The ingested embryos bore their way through the wall of the bowel, and are carried to the liver by the portal vein. Here they develop into the larval or cysticercus stage. The cyst wall is composed of a laminated membrane rather like the white of an egg, lined by a germinal layer from the cells of which daughter cysts grow. Scolices or heads of new individuals are formed within the cysts, and these are armed with a row of small hooklets. The nature of the cyst can be recognized from the microscopic appearance of the laminated membrane, or the presence of the tiny hooklets in the watery fluid.

The liver may be greatly enlarged, and the mass caused by the large cysts is easily mistaken clinically for a tumor. The larvæ die out after

some years, and the cyst may be converted into a putty-like mass with calcification of the capsule. Rupture may occur into the abdominal or pleural cavity, and the fluid may produce toxic effects. The fluid may be used as an antigen in a complement-fixation test or a precipitin test for the disease.

**OTHER PARASITES.**—In schistosomiasis the ova may be carried by the portal blood stream to the liver, where they may set up a rather characteristic form of cirrhosis with areas of dense white connective tissue around the portal tracts. This is particularly liable to happen with *S. mansoni* and *S. japonicum* infections, as these flukes inhabit the mesenteric veins. The cirrhosis may be associated with carcinoma of the liver. The liver fluke, *Clonorchis sinensis*, invades the bile ducts in large numbers and may cause jaundice.

## DEGENERATION OF THE LIVER

**Fatty Infiltration.**—So-called fatty degeneration of the liver has already been considered in Chapter 2. It is really an infiltration, fat being carried from the fat depots to the liver where it fails to be metabolized for various reasons. Accumulation of fat in the liver is one of the most delicate indicators of interference with the health of the organ. It is marked in diabetes, pernicious anemia, chronic alcoholism, etc. Starvation induces the condition, thus explaining in part the frequency with which it is found in hospital autopsy material. The part played by lipotropic factors in the experimental production of accumulation of fat in the liver has already been discussed on page 498. Extensive replacement of liver cells by fat in heavy drinkers may be the cause of entirely unexpected and abrupt death (Le Count and Singer). The liver is huge, and the liver cells are represented by large fat globules. Replacement of glycogen is the probable cause of death. The fatty liver is yellow in color and greasy to the touch. The fat is either in the form of one large globule which pushes the nucleus to one side, or of many tiny droplets scattered through the cytoplasm. The latter probably indicates a greater disturbance in the health of the cell. Hartroft has shown that the huge globules really represent fat cysts formed by the fusion of many fat-filled cells to form one large globule of fat (see page 499).

**Amyloid Degeneration.**—Amyloid disease is described in Chapter 2. The spleen and the kidney are involved as well as the liver. The liver is much enlarged, smooth, and firm and elastic in consistence. The cut surface has a characteristic translucent (waxy) look, with brown amyloid patches when treated with iodine. The essential change is an extreme hyaline (amyloid) swelling of the connective tissue, as a result of which the liver cells undergo a pressure atrophy and largely disappear. The veins and sinusoids are also compressed, yet ascites is a rare occurrence though sometimes it does develop. There is no jaundice. In advanced cases the microscopic changes are so extreme and the replacement of liver cells so great that it is remarkable that there is so little disturbance of liver function.

**ATROPHY.**—This is most marked in inanition, and in chronic starvation the liver may be quite shrunken and of a uniform brown color with loss of lobulation. In old age some atrophy is common. Pressure of a tumor, of amyloid deposits, etc.,

may produce local atrophy. Tight lacing (in the past) or continual stooping (occupational) may lead to the formation of grooves on its upper and anterior surface. There may be deep sagittal furrows corresponding to bulgings of the diaphragm.

**POSTMORTEM CHANGES.**—The commonest change is a bluish or greenish *discoloration* of the surface, due to the action of hydrogen sulphide liberated from the intestine and similar to the postmortem discoloration of the abdominal wall. It is seen first in those parts of the liver in contact with coils of intestine. *Foamy liver* is a condition in which the organ is filled with bubbles of gas, which are produced after death by gas-forming bacilli. It may resemble a sponge. The condition is most likely to occur in wound infections with the anaerobic gas-producing bacteria.

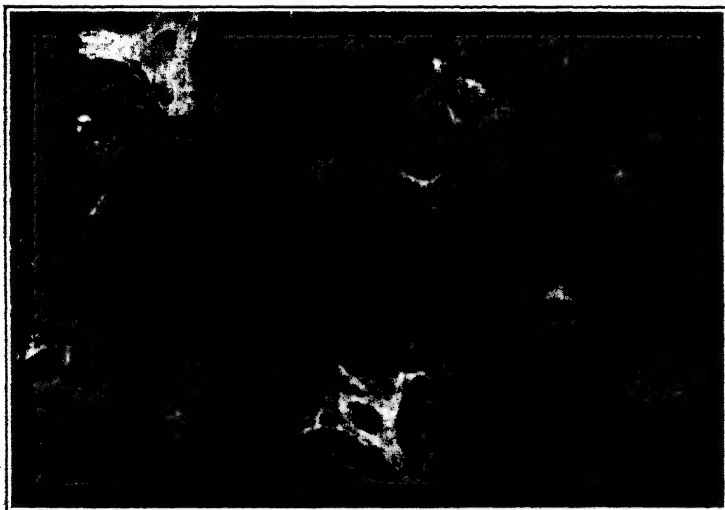


FIG. 286.—Nutmeg liver showing a combination of chronic venous congestion and fatty degeneration.

### CIRCULATORY DISTURBANCES OF THE LIVER

**Chronic Venous Congestion.**—No organ shows chronic congestion so often as the liver, because when there is any back pressure on the venous circulation it is the hepatic vein which feels it first, as it practically opens into the right auricle. The common cause is valvular disease of the heart or myocardial failure. Emphysema which narrows or obliterates the pulmonary capillaries causes distention of the right side of the heart, and this is followed by congestion of the liver.

The liver is enlarged so that it can be felt below the costal margin, firm, and as the capsule is tightly stretched it may be painful and tender. In the later stages it may become smaller owing to atrophy of the parenchyma. The cut surface shows the characteristic appearance known as *nutmeg liver*, characterized by undue distinctness of the lobules and a mottling with dark and light areas (Fig. 286). The central vein and the surrounding sinusoids are filled with blood so that the center of the lobules is dark red; the periphery is pale because the cells are fatty and swollen,

and the congestion of the sinusoids is much less there. *Microscopically* the central vein and the sinusoids of the central area of each lobule are so distended with blood that the liver cells may have largely disappeared owing to pressure atrophy. At the periphery of the lobule the congestion is usually much less marked, and the liver cells are fairly intact, but they show a considerable degree of fatty degeneration owing to the poor oxygenation. As the condition progresses the connective tissue stroma proliferates, giving *cardiac cirrhosis*. The distribution is essentially the same as in portal cirrhosis.

**INFARCTION.**—True infarction of the liver is a remarkably rare occurrence. Pseudo-infarcts are much commoner. The latter are generally hemorrhagic, and are really localized areas of venous engorgement, but they may be anemic. The distinction between true and false infarcts depends on the presence or absence of necrosis, so that it can only be made with the aid of the microscope. There are various reasons for the rarity of true infarcts. (1) The liver has a double blood supply from the hepatic artery and the portal vein. (2) About 65 per cent of the blood is supplied by the portal vein, and cutting off this venous blood is not likely to have the same effect on the liver cells as the loss of arterial blood; I have seen complete thrombosis of the portal vein without any apparent damage to the liver. (3) The liver cells are accustomed to a condition of relative anoxia, and they can resist temporary ischemia caused by ligation of the hepatic artery and portal vein for six to twelve hours. (4) Unnamed collateral vessels pass from the diaphragm into the liver. (5) The hepatic artery does not arise directly from the aorta. The chief causes of infarction are embolism of the hepatic artery and periarteritis nodosa affecting that vessel, both very rare conditions. The infarct tends to remain red, but it may become pale. *Traumatic infarction* is a condition in which the blood supply to a portion of the liver is cut off as the result of laceration from crushing injuries. The affected part undergoes a coagulative necrosis and has a dull yellow appearance. The condition is rare because the patient is likely to die of hemorrhage into the peritoneal cavity.

**PORTAL THROMBOSIS.**—Thrombosis of the portal vein may complicate cirrhosis and primary carcinoma. Sometimes it is the result of a chronic phlebitis. The wall of the vein usually shows evidence of sclerosis. When the main vessel is filled by a thrombus there will be very marked and rapidly recurring ascites, enlargement of the spleen, and other signs of portal obstruction.

**HEPATIC VEIN THROMBOSIS.**—This rare condition may be due to a tumor extending into the vein, to portal cirrhosis, and sometimes to no obvious cause. I have seen a case in which thrombosis followed three weeks after an abortion. The chief effects are pain and swelling of the liver and ascites.

## CONGENITAL ANOMALIES OF THE LIVER

In rare cases one lobe of the liver may be absent or the left lobe may be very small. *Riedel's lobe* is a downward prolongation of the right lobe which may be mistaken for an abdominal tumor. *Cystic liver* is probably a congenital condition, although it is usually seen in the adult. It is associated with the much commoner congenital cystic kidney, but the latter usually occurs without any cysts in the liver. Sometimes there are cysts in the pancreas. The cysts in the liver may be few and small, or the whole liver may be studded with large and small cysts so that the organ is greatly enlarged. In this case there will be great pressure atrophy of the liver parenchyma. As in the case of the cystic kidney the cysts tend to enlarge gradually. They contain a clear albuminous fluid and are lined by cubical epithe-

lium. The condition is supposed to be due to some malformation of the smaller bile ducts, which fail to become connected with the main biliary tree and undergo cystic dilatation. Occasionally other congenital abnormalities such as hydrocephalus, spina bifida, and talipes may be present.

## JAUNDICE

The liver has far more important functions than the excretion of bile, but at present the estimation of those functions is a matter of great difficulty, and the study of the behavior of the bile pigments affords one of the most convenient methods for determining the state of health or disease of the liver cells. For this reason the study of jaundice or icterus is of interest to the pathologist as well as to the clinician. Jaundice is a coloration of the skin and sclerotics by bile pigment in the blood. The color varies from pale yellow to deep orange or even green. The internal organs are pigmented with the exception of the central nervous system, which usually escapes.

Bilirubin is formed from the hemoglobin of broken-down erythrocytes by the cells of the reticulo-endothelial system, principally those of the bone-marrow and spleen. If hemolysis is increased the amount of bilirubin formed will be correspondingly increased. The bile acids are synthesized only by the liver.

When the bilirubin is formed it is carried to the liver for excretion. There are three elements in a liver lobule: (1) the hepatic cell; (2) the bile canaliculus, which we may call the bile duct; and (3) the sinusoid, which connects the portal with the hepatic vein and is lined intermittently by Kupffer cells (Fig. 287). The hepatic cell is flanked on one side by the vessel, on the other side by the bile duct. The bilirubin is carried to the lobule by the blood, passes through the wall of the vessel, is excreted by the hepatic cell into the bile duct, and escapes into the intestine. In the large bowel it is reduced by bacterial action to urobilinogen which is colorless. The greater part of the urobilinogen is excreted in the feces, but part is absorbed into the portal circulation and passes to the liver. Part of this fraction is again excreted by the hepatic cells, but part passes on into the general circulation and is excreted in the urine. In health a very small but fairly constant amount of urobilinogen is present in the urine. When bilirubin has passed through the hepatic cells it is affected by the bile acids, possibly by direct coupling. If the altered bilirubin is then reabsorbed into the blood, as in obstructive jaundice, it is able to pass the barrier of the renal filter and appears in the urine. If it has not passed through the hepatic cells it is held up by the renal barrier and does not enter the urine, even though the amount in the blood is sufficient to produce jaundice; this is known as acholuric jaundice.



FIG. 287. —Swollen and detached Kupffer cells in liver sinusoids.  $\times 525$ .

The most rational classification of jaundice is based on the relation of the bilirubin to the liver cell. The lesion responsible for the jaundice may be *before, in, or after* the bilirubin has passed through the liver cell, the result being respectively hemolytic, hepatic, or obstructive jaundice. The first two may be grouped together as retention jaundice, the liver being unable to excrete all the bilirubin, which therefore accumulates in the blood. This inability may be due to too much bilirubin being produced (hemolytic jaundice), or to sickness of the liver cells preventing them from excreting the normal amount of bilirubin (hepatic jaundice). For a further discussion of these matters and a consideration of what he calls regurgitation jaundice, Rich's excellent paper should be consulted.

Of the great numbers of liver function tests, two are of special value in the study of a case of jaundice. A negative cephalin-cholesterol flocculation test shows that there is no primary disease of liver cells, and that the jaundice is not due to a hepatitis. A *high* alkaline phosphatase reading indicates obstruction either in the large bile ducts or hepato-cellular in character.

1. **OBSTRUCTIVE JAUNDICE.**—The purest examples of obstructive jaundice are cases of obstruction of the common bile duct by cancer of the head of the pancreas, stone in the duct, or stricture of the duct. The pigment passes through the liver cells, but as it cannot escape, it is reabsorbed into the blood, produces clinical jaundice, and flows over into the urine. The *congenital jaundice* of children (not icterus neonatorum) due to atresia of the biliary passages belongs to this group. When the obstruction is severe little or no bile passes into the intestine, and the stools are *clay-colored*, because the fats remain undigested in the absence of bile. Owing to this absence no urobilinogen is formed, and as none is absorbed the urobilinogen normally present in the urine disappears completely.

2. **HEMOLYTIC JAUNDICE.**—When there is excessive hemolysis the bilirubin carried to the liver cannot be all excreted so that some remains in the blood. This type of bilirubin cannot pass the kidney filter, so that the jaundice is of the acholuric type although there is a great increase of urobilinogen in the urine. The jaundice is never so intense as it may become in the obstructive form. This form of jaundice is best seen in the disease known as hemolytic jaundice (also called acholuric jaundice), in which there is overactivity of the reticuloendothelial system and increased fragility of the red blood cells, as a result of which the amount of hemolysis is considerably above normal. As might be expected, the amount of urobilinogen excreted in the feces is greatly increased.

Lesser degrees of jaundice may occur whenever there is marked hemolysis, *e.g.*, as the result of snake-bite, intraperitoneal hemorrhage, large pulmonary infarcts, ruptured tubal pregnancy, and blood infection with hemolytic streptococci. Sometimes, as in pernicious anemia, the blood bilirubin may be above normal as shown by the icterus index, but below the amount necessary to produce clinical jaundice. This is known as latent jaundice.

3. **HEPATIC JAUNDICE.**—This form, also called toxic jaundice, is the jaundice of infectious (virus) hepatitis, or, more accurately, of liver necrosis. Hepatocellular jaundice is perhaps the most descriptive term for the condition. The first effect of disease of the hepatic cells is an inability to excrete all the bilirubin, some of which therefore accumulates in the blood. An even earlier result is a retention in the blood of the urobilinogen brought from the bowel, and a corresponding increase of the urobilinogen in the urine. With continued action of the virus the hepatic cells become more and more swollen so as to cause obstruction of the tiny bile canaliculi whose walls they form. Some of the bilirubin still passes through the sick cells, but as it cannot escape on account of the blockage of the canaliculi it is reabsorbed. If the chief effect of the lesion is retention, the bilirubin will not appear in the urine. If there is much obstruction of the canaliculi this reabsorbed bilirubin will accumulate in the blood and flow over into the urine. The milder



forms constitute the common catarrhal jaundice. In the most extreme forms little or no bile may enter the intestine. In this case the stools will be clay-colored, and the urobilinogen in the urine will first diminish and finally disappear altogether.

*Symptoms of Jaundice.*—The principal symptoms are due to a retention of bile salts rather than to the bile pigment. In the disease known as hemolytic jaundice where the liver cells are normal there is no retention of bile salts, so that there are none of the characteristic symptoms. Such a dissociation between bile salts and bile pigment is spoken of as dissociated jaundice. In obstructive jaundice the salts as well as the pigment are retained, and the patient suffers from severe and sometimes uncontrollable itching, bradycardia (slow pulse), hemorrhage due to injury of the capillary endothelium by the bile salts, and various nervous symptoms. The blood cholesterol, which should normally escape in the bile, is increased, and there may be deposits of cholesterol in the skin which form small yellow nodules known as xanthomata. Bleeding is an important feature of jaundice, and postoperative bleeding may prove fatal. It is due to a marked fall in the plasma prothrombin, associated with prolonged clotting time. The low prothrombin level is due to: (1) failure of absorption of vitamin K from the intestine owing to absence of bile; (2) damage to the liver, in which organ prothrombin is formed from vitamin K. Administration of synthetic vitamin K before operation will bring the prothrombin level back to normal and prevent hemorrhage. In catarrhal jaundice there is a characteristic leucopenia or diminution in the white cells of the blood, which often fall to 4000 per c.mm. and sometimes even to 2000. The chief decrease is in the polymorphonuclears.

*ICTERUS NEONATORUM.*—Some degree of jaundice is very common in the newly-born. This is merely an exaggeration of a physiological condition present in all infants after birth. The jaundice is therefore hemolytic in type, and may remain latent or become visible. The reason for the hemolysis is that the child at birth has a polycythemia, an excessive number of red blood cells, because *in utero* it has been living in a condition of anoxemia or constant lack of oxygen. After birth the need for the polycythemia ceases, the excess red cells are destroyed by hemolysis, an increased amount of bilirubin is produced, and there is jaundice either latent or clinical.

*WEIL'S DISEASE. SPIROCHETOSIS ICTEROHEMORRHAGICA.*—Weil's disease is a very acute epidemic infection, characterized by marked jaundice, hemorrhages from the mucous membranes, fever, enlargement of the spleen and nephritis. There is marked evidence of blood destruction, and blood and bile appear in the urine. The disease is caused by a specific spirochete (*Spirochæta icterohaemorrhagiae*). It occurs in troops on active service, and workers in mines, sewers and abattoirs. The factors common to these occupations are dampness of the soil and close association with rats.

The rat seems to act as a reservoir of infection, excreting great numbers of spirochetes in the urine. The spirochetes may penetrate the skin directly. Fleas may act as an intermediate host. A few cases have been caused by rat bites. The disease usually lasts about three weeks. During the first week the spirochetes are present in the blood. In the second week they disappear from the blood, but appear in the urine.

In addition to cloudy swelling the liver may show small areas of focal necrosis, in which mitoses or amitotic division can be seen. Even more striking than mitoses is the presence of binucleated liver cells, as if amitotic division of the nucleus had occurred. In some cases there is a striking dissociation of liver cells, the columns being broken up and the cells separated from one another (Fig. 288). The renal tubules show degeneration or actual necrosis. There are degenerative changes in the muscle fibers, especially in the legs, and focal ischemic necrosis in the brain. The spirochetes, which often present a terminal hook like a shepherd's crook (Fig.

289), lack the sharp spirals of the spirochete of syphilis. They are present in large numbers in the liver, kidney and adrenal, and in smaller numbers in other organs. If a guinea-pig is inoculated with blood during the first week or with urine during the second week it will develop the disease and will show hemorrhages in the lungs and enormous numbers of spirochetes in the liver and kidney. Some strains, however, are not pathogenic for guinea-pigs. The patient's urine may also be examined directly for spirochetes by the dark-field method. Immune bodies are developed in the blood, so that an agglutination test is of value for diagnosis.

**CANICOLA FEVER.**—This rare condition may be considered here because of the relation of the infecting spirochete to that of Weil's disease, but there is neither jaundice nor involvement of the liver. The organism is *Leptospira canicola*, so-called because the carrier host is canine, not rodent. The symptoms suggest involvement of the central nervous system, and the cases may be mistaken for



FIG. 288.—Dissociation of liver cells in Weil's disease.  $\times 300$ .



FIG. 289.—Spirochete in kidney in Weil's disease.  $\times 1350$ .

meningitis or poliomyelitis. Both the protein and cell count of the cerebrospinal fluid are increased. Some degree of nephritis is almost always present, and the urine may contain albumen, casts, and red blood cells. Fever continues for about a week. The prognosis is good.

## THE GALL-BLADDER

The normal gall-bladder is 3 to 4 inches long, and its capacity is about 45 cc. The liver produces nearly a liter of bile a day, but only some of this reaches the duodenum. The rest is absorbed, or rather the watery part is absorbed, by the wall of the gall-bladder, so that the bile is greatly concentrated. The inner surface of the gall-bladder appears to be designed for absorption. The entire surface is divided into a series of polygonal spaces by delicate walls of mucous membrane, which are best appreciated if the gall-bladder is examined under water by means of a magnifying glass or a binocular dissecting microscope. When this is done the transparent

mucous folds, gossamer-like in delicacy, are seen to float up like leaves of a water plant in a clear pool.

A peculiar feature of the gall-bladder, pointed out by McKibbin and McDonald, is that polymorphonuclear leucocytes are frequently present in one or more layers of the organ without any other evidence of inflammation. These cells are also present in the dog's gall-bladder. They do not indicate inflammation, and appear to be metabolic in function.

The muscle coat ceases abruptly at the neck of the gall-bladder, and the bile ducts (cystic and common) are fibro-elastic tubes with only a few isolated muscle fibers. There is an abundance of nerve fibers in the outer part of the wall of the ducts. From these facts it is evident that biliary colic is due to distention of the duct and not to muscular spasm.

### CHOLECYSTITIS

**ETIOLOGY.**—Occlusion of the cystic duct is probably the most important single factor in the production of acute cholecystitis (Andrews). The lumen of the duct is small, and its wall is thick and deeply pocketed with sinuses, so that a slight degree of inflammation will cause narrowing or closure of the duct. Calculi causing obstruction may be associated either with acute or chronic inflammation. The intensity of the ensuing inflammation depends on the composition of the imprisoned bile (Womack and Bricker). When the cystic duct is tied after the gall-bladder has been emptied and washed with saline, no inflammation develops. When the gall-bladder contains bile there is edema, round-cell infiltration and fibrosis. When the bile is replaced by a solution of dried bile double the concentration of that of normal bile, the wall undergoes complete necrosis, although when the cystic duct is open the changes are slight and transient. It is reasonable to suggest that in chronic as well as in acute cholecystitis the chemical factor is of great importance. This would serve to explain the extreme diffuseness of the lesions so different from the patchy focal lesions of chronic inflammation in other organs, and also the association of cholecystitis with gall stones which are an important cause of biliary obstruction.

**Acute Cholecystitis.**—The wall of the gall-bladder is thickened, the serous surface is congested and covered by a fibrinous exudate, and the mucosa is bright red or purple. When obstruction of the cystic duct is complete the lumen is distended with what appears to be purulent fluid, so that the condition is known as *empyema of the gall-bladder*. This is often not a true empyema, for the "purulent" fluid is frequently found to consist of an emulsion of cholesterol crystals. *Microscopically* the most striking picture is a marked inflammatory edema, which is responsible for most of the thickening. Polymorphonuclears are relatively few in number in striking contrast to the abundant purulent exudate in acute appendicitis, suggesting a non-bacterial inflammation. Reference has already been made to the presence of polymorphonuclear leucocytes in the uninflamed gall-bladder. In some cases the picture is that of an ordinary purulent inflammation, and in these the bacterial count in the bile is enormously increased.

**Chronic Cholecystitis.**—Chronic cholecystitis may be the result of an acute attack, but usually it is chronic from the outset and the symptoms develop gradually and insidiously. There is a low-grade inflammatory reaction commencing in the outer part of the wall and gradually spreading throughout the gall-bladder. The gross appearance varies considerably. The bluish color of the thin-walled normal gall-bladder is lost, and the surface may be opaque; it is sometimes yellow owing to an accumulation of subserous fat. The wall is thickened and fibrosed (Fig. 290), and the cavity may be of normal size, dilated or contracted. If there has been no obstruction at the neck of the gall-bladder, the cavity is likely to be small from contraction of the new fibrous tissue. Sometimes the gall-bladder is contracted upon one or two large stones, so that no room is left for any bile.



FIG. 290.—Chronic cholecystitis. The gall-bladder is dilated, its wall moderately thickened, the fundus contains a large calculus, and the lining shows reticulation.

Should obstruction be present owing to inflammatory swelling, cicatricial contraction, or the impaction of a stone at the neck of the bladder, there will be dilatation of the cavity as well as thickening of the wall. If obstruction becomes marked before the inflammatory changes have had time to cause thickening, the wall of the greatly dilated bladder may be quite thin. The cavity is filled with clear, colorless, watery fluid secreted by the lining epithelial cells, a condition known as *hydrops* of the gall-bladder. The bile pigment is absorbed, and no more can enter owing to the obstruction. The condition of the gall-bladder depends on the balance between inflammation and obstruction. In the milder cases the surgeon may have great difficulty in deciding at operation whether or not the gall-bladder is diseased and should be removed. The cystic gland at the neck of the gall-bladder is usually enlarged.

When the gall-bladder is opened the appearance again varies. The color is usually not much changed, but it may be a deep red. With a hand lens or the dissecting microscope the thin folds of the normal mucosa are seen to be thick and swollen, but when the organ is markedly distended as in hydrops they may disappear completely. It is evident that the absorbing and concentrating power of the gall-bladder will be greatly impaired or lost, so that no shadow is seen with Graham's visualization test. As a result of contraction of the fibrous tissue the surface may become reticulated and scarred, so as to present an interlacing network of fine bands which show through the atrophic mucosa with great distinctness.

The *microscopic appearance* is one of chronic inflammation usually involving the entire organ. There are definite groups of lymphocytes, and occasionally large numbers of plasma cells and eosinophils, as well as a more diffuse infiltration. Single sections are of doubtful value, for serial sections show a high degree of patchiness of infiltration, which is often more marked on the hepatic than on the peritoneal surface. The folds of mucosa are thickened owing to edema. It must be remembered that the normal

mucosa contains large numbers of round cells; these must not be mistaken for an inflammatory infiltration. The epithelium is usually intact in well-fixed tissue. Postmortem material is useless as, immediately after death,



FIG. 291.—Chronic cholecystitis. The wall is greatly thickened and groups of inflammatory cells are scattered through it. The muscle is largely replaced by fibrous tissue.  $\times 40$ .

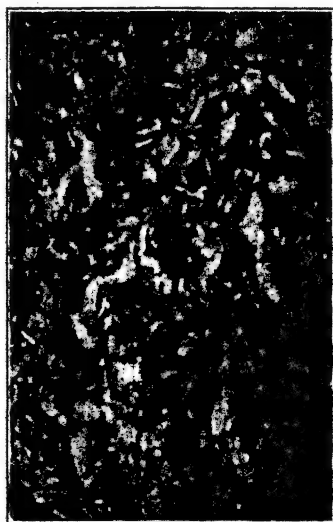


FIG. 292.—Cholesterolosis of the gall-bladder under the dissecting microscope. The ridges of mucosa are loaded with lipid.

the bile digests away the epithelial lining in both the normal and pathological gall-bladder. The same is true, though in a lesser degree, of gall-bladders removed at operation unless they are at once opened and placed in formalin. The very best results are obtained by distending with formalin the freshly removed and emptied gall-bladder. In the later stages there is an abundant formation of granulation tissue which causes great thickening of the wall (Fig. 291), and is ultimately replaced by fibrous tissue, so that the gall-bladder is converted into an inert bag incapable of contraction. There may be a marked increase in the amount of elastic tissue, which

normally is quite scanty (Riopelle). The elastic tissue increases both with age and with the duration of the disease. The increase seems to be dependent on intermittent dilatation of the viscus, and ceases after complete obstruction develops. It is comparable to the elastosis of benign hypertension.

**CHOLESTEROSIS OF THE GALL-BLADDER.**—This is also known as the *lipid gall-bladder* and the *strawberry gall-bladder*. The wall is usually a little thickened, but the most striking change is in the mucosa, over the surface of which are scattered little yellow flecks like the seeds of a strawberry. The condition is best seen with the hand lens or under the dissecting



FIG. 293.—Cholesterosis of the gall-bladder. There are large masses of cholesterol in the mucosa and also in the deeper parts of the wall. A pedunculated mass is almost separated from its attachment. (From Boyd's Surgical Pathology.)

microscope, which gives a much better idea of the lesion than a microscopic section (Fig. 292). The normal delicate mucosal folds are seen to be loaded down by opaque yellow masses which first appear on the summit of the ridges. These are deposits of cholesterol ester which can be studied in frozen sections stained with a fat stain (Scharlach, osmic acid), or under crossed Nicol's prisms where their anisotropic character is revealed. The lipid is found at the base of the epithelial cells of the mucosa and in phagocytic histiocytes in the deeper part of the wall. A mass of lipid in the mucosa may become pedunculated and is then readily detached, when it may act as the nucleus around which a gall stone may be formed (Fig. 293 and Plate XIV).

The explanation of the condition is not easy. Cholesterol seems to be absorbed by the gall-bladder mucosa, although Elman and Graham believe that it is excreted, and that the excretion is increased by inflammation. In the condition of cholesterosis there is storage of cholesterol under the

## PLATE XIV



Polypoid Mass of Cholesterol Ready to Separate.  
Early case of strawberry gall-bladder. Stained with Scharlach R.  
(*Boyd's Surgical Pathology, courtesy of W. B. Saunders Company.*)

mucosa. Two possible etiological factors may be at work. The first and most important is a disturbance of cholesterol metabolism, as a result of which the amount of cholesterol in the blood and bile is increased. The second is a mild degree of chronic inflammation. It is probable that the condition of cholesterolosis is not necessarily a permanent one, and that most if not all the cholesterol may finally disappear. There is no convincing evidence that these deposits can cause symptoms or that they are of any clinical significance.

**CHOLECYSTITIS GLANDULARIS.** — Sometimes, apparently as the result of chronic irritation, the epithelium lining the gall-bladder commences to proliferate and form gland-like spaces. This proliferation may take the form of a papillary projection, commonly called papilloma of the gall-bladder. In other cases the growth is into the depth of the wall and new glands are formed which may penetrate the entire thickness of the wall and form a mass on the serous surface (Fig. 294). An apparent diverticulum or pocket may thus be formed, and its communication with the lumen of the gall-bladder may or may not be apparent. These various appearances are merely an exaggeration of the structures known variously as Luschka's crypts and Rokitansky-Aschoff sinuses, which Robertson and Ferguson point out are merely diverticula of the gall-bladder, similar to the diverticula occurring in the colon and urinary bladder. They are protrusions of the mucosa through the muscular coat, invaginations which are found in about half of all gall-bladders removed in persons over thirty years of age.

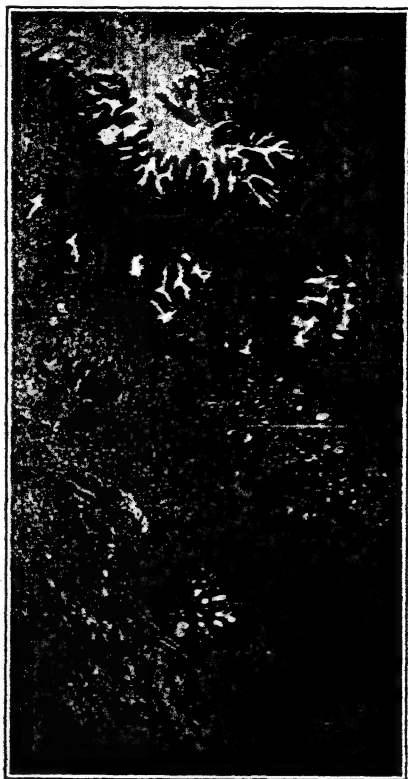


FIG. 294. — Formation of new glands in whole thickness of gall-bladder wall.

## GALL STONES

Gall stones or biliary calculi are usually formed in the gall-bladder, but may be formed in the bile passages, especially those within the liver. They may be single or multiple; sometimes there are several hundred small stones. There are three constituents: cholesterol, bilirubin, and calcium. As the proportion of these varies, so do the calculi vary in their gross appearance. Three main varieties may be recognized: (1) the pure cholesterol stone, (2) the pure pigment stone, and (3) the common infective or mixed stone.



**ETIOLOGY.**—The etiology of gall stones is still unsettled. We are certainly powerless to prevent their formation. Three factors may play a part: infection, stasis, and high bile cholesterol. It does not follow that all three need be present in any given case. (1) *Infection*. This is the principal factor. All the infective or mixed stones are associated with cholecystitis. The cholecystitis causes the calculi, not *vice versa*. Cholesterol is held in solution in the bile in a series of loose chemical complexes with bile salts. These may easily be broken up, *e.g.*, by dialysis. When the bile salts are removed the cholesterol is precipitated. There is no differential absorption of cholesterol and bile salts by the normal gall-bladder. The infected gall-bladder, on the other hand, absorbs bile salts rapidly but

cholesterol very slowly, so that the latter tends to be precipitated. When a nucleus of cholesterol is established bilirubin is laid down around it to form a mixed stone. (2) *Stasis* probably plays a part. In pregnancy the gall-bladder does not empty in response to a fat meal. Gall stones are much commoner in women (3 or 4 to 1), especially in those who have borne children. Patients with gall stones are often "fat, female, and forty." (3) *High bile cholesterol*, associated in turn with high blood cholesterol, is a possible factor, although the hypercholesterolemia may have disappeared by the time symptoms have begun to manifest themselves. Deposits of cholesterol in the mucosa may become pedunculated, detached, and form the starting-point of calculi.

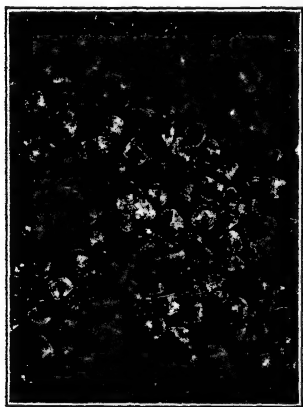


FIG. 295.—Infective gall stones. The faceted stones are very uniform in size.

**PURE CHOLESTEROL STONE.**—This is also called the *metabolic stone*, because it is essentially due to a disturbance of cholesterol metabolism. It is large, oval, white, usually single, of light weight, and the cut surface shows a characteristic radiate structure and glistening crystals of cholesterol. The factors which favor its formation are high bile cholesterol and stasis in the gall-bladder. It is a silent stone and usually causes no symptoms. There is no change in the gross appearance of the gall-bladder. The stone may become impacted in the neck of the gall-bladder and lead to a condition of hydrops. Sometimes the impaction is followed by infection. Should the stone now roll back into the gall-bladder and allow bile to enter, bilirubin calcium is deposited on the surface and a *combination stone* is formed.

**PURE PIGMENT STONE.**—These stones are multiple, very small, black in color, friable, and consist of bilirubin. They contain no cholesterol. They are often present in hemolytic jaundice, but are not confined to that condition. Like the previous stone they appear to be metabolic in origin. When very small and numerous they constitute biliary gravel.

**INFECTIVE OR MIXED STONES.**—This is the common variety, composed of cholesterol, bilirubin, and calcium. The pigment and cholesterol are laid down in alternate layers, so that the cut surface presents a concentric arrangement of laminae. The general color is yellow or brown, and the stones are faceted and polished unless there is only one (Fig. 295). There may be two or three families of stones, all the members of each family being about the same size and probably starting life at the same time. In the center there is usually a nucleus of mucus and cellular debris.

The effect on the gall-bladder varies with the kind of stone, for the changes are due to inflammation. The metabolic stones (cholesterol and pigment) are likely to be associated with a gall-bladder which appears normal unless

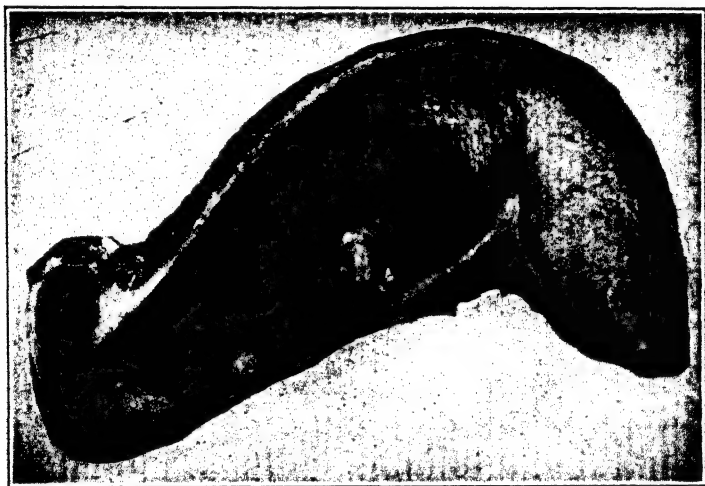


FIG. 296.—Facetted calculi in gall-bladder with moderately thickened wall.

the stone causes obstruction. The infective stone is associated with cholecystitis, so that the wall will be thickened and the lumen usually contracted, but dilated if impaction has occurred early (Fig. 296). Stone in the common duct is seldom associated with dilatation (see below). The pressure of a stone may produce ulceration so that a deep pocket is formed. This may perforate the wall, and the stone escapes into the peritoneal cavity or into a cavity walled off by adhesions. If the gall-bladder becomes adherent to the bowel the stone may perforate into the transverse colon or into the ileum.

**THE RELATION OF SYMPTOMS TO LESIONS.**—Cholecystitis and calculi will be considered together. In *acute cholecystitis* the severe pain and tenderness over the gall-bladder are explained by the acute inflammatory swelling and tension of the wall. There may be some jaundice owing to spread of the inflammation to the common bile duct with obstruction. *Biliary colic* is due to the passage of a small stone along the cystic and common bile ducts, causing distention of these passages. There is probably no spasm owing to the absence of muscle fibers. Colic is not a certain proof of a stone, for the passage of masses of pus or mucus may also produce colic.

The mere presence of stones in the gall-bladder may or may not be associated with symptoms. Stones are often found at postmortem when the patient had no symptoms to suggest gall-bladder disease. When symptoms do occur, they are due to the associated cholecystitis. The metabolic pure cholesterol stone is silent.

The symptoms of *chronic cholecystitis* are for the most part referable to the stomach, i.e., dyspepsia, nausea, belching of gas, and a feeling of fulness and bloating. These symptoms are aggravated by fatty foods. Food containing much fat causes the gall-bladder to contract and empty itself, and if the wall is inflamed this may cause discomfort. The stomach suffers because it has the same double nerve supply (vagus and sympathetic from the ninth dorsal segment) as the gall-bladder, and appears to be a specially sensitive and, as it were, sympathizing organ.

It seems improbable that *cholesterolosis* of the gall-bladder can of itself give rise to symptoms. The condition is not infrequently found at autopsy in persons who have never had any symptoms of gall-bladder disease.

### OBSTRUCTION OF THE BILIARY PASSAGES



Fig. 297.—Thick secretion of mucus in gall-bladder with obstructed cystic duct.  $\times 85$ .

The biliary passages may be obstructed in different ways and at different levels. The effect varies with these differences. *Courvoisier's law*, now a hundred years old, states that in jaundice due to pressure on the common bile duct from without, as by cancer of the head of the pancreas, the gall-bladder is greatly distended, while in jaundice due to impaction of a stone in the common duct the gall-bladder is not distended to such an extent that it can be detected clinically. This is a useful working rule which still holds good. The reason is that in obstruction due to stone there is already a cholecystitis, the wall of the gall-bladder is thickened, so that it cannot be greatly distended; indeed it may be considerably contracted. It is important to remember that many stones may be lodged in the common duct; I have seen as many as 25 in one case, the gall-bladder containing 23 more.

The site of the obstruction has an influence on the contents of the dilated ducts. (1) If the obstruction is in the common duct (the usual site) the biliary passages are still in free communication with the gall-bladder, which concentrates the bile retained in the passages so that it becomes thick and dark. (2) If the obstruction is above the entrance of the cystic duct this concentrating mechanism can no longer operate, the bilirubin is absorbed, and the epithelial cells lining the hepatic ducts secrete a clear watery fluid, the so-called *white bile*, which fills and distends the biliary passages. It is evident that this fluid is not bile at all. If the wall of the gall-bladder is degraded by disease so that it loses its concentrating power, an obstruction in the common duct will produce the same effect as if it was above the entrance of the cystic duct, and the entire biliary tract, including the gall-bladder, will become filled

with "white bile." (3) If the cystic duct is blocked by an impacted calculus or a tumor, the bile in the isolated gall-bladder is first absorbed, and is then replaced by clear fluid secreted by the lining epithelium. This fluid is much more mucoid than that secreted by the lining of the hepatic ducts, and the condition is called *mucocoele* or *hydrops* of the gall-bladder (Fig. 297).

### CARCINOMA OF THE GALL-BLADDER

Cancer of the gall-bladder is a relatively common condition. This is not surprising when it is recalled that derivatives of cholic acid are amongst the most powerful of the chemical carcinogens. It bears a close relationship to the presence of gall stones, seldom occurring apart from calculi, so that the disease is four or five times commoner in women than in men. It thus offers a striking exception to the general rule that cancer of the digestive tract is much more common in the male sex.

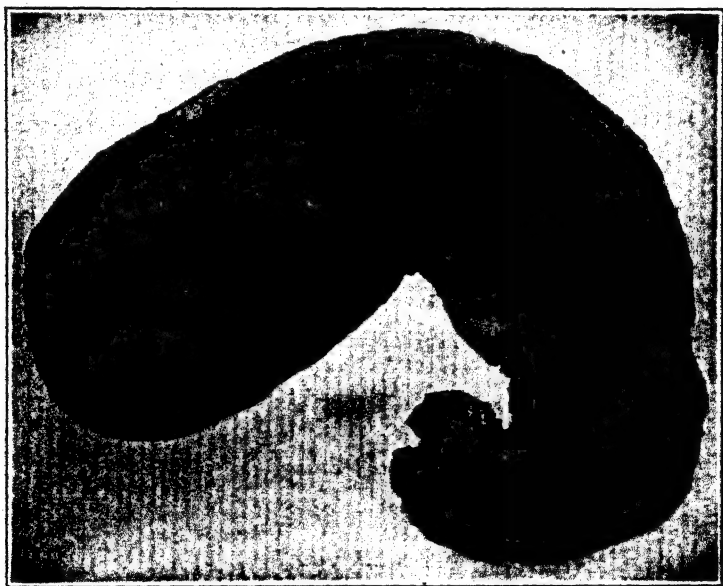


FIG. 298.—Papillary carcinoma at neck of gall-bladder.

The usual sites are the fundus and the neck of the gall-bladder. It takes an infiltrating form, causing great thickening of the wall, but sometimes there is a large soft papillomatous mass which projects into the cavity of the organ (Fig. 298). *Microscopically* the structure is that of an adenocarcinoma, but in rare cases it may be that of an epidermoid carcinoma, owing to metaplasia of the columnar into squamous-cell epithelium from the chronic irritation which precedes the development of the tumor. The liver is invaded early, and jaundice is a constant symptom.

*Carcinoma of the bile ducts* usually grows at the lower end of the common duct, where it forms a small, hard, white mass readily mistaken for an

impacted calculus. It is a rather rare condition, and is usually adenocarcinomatous in structure.

**LIVER DEATH.**—It sometimes happens that cholecystectomy, operations on the bile ducts, or traumatic injury to the liver, is followed after a latent interval by sudden and extreme hyperpyrexia ending in death. These cases may be divided into two groups; in the first hyperpyrexia develops in twenty-four to forty-eight hours, and the only lesion is degeneration (sometimes necrosis) of the liver cells; in the second the symptoms do not develop for four to five days, the clinical picture is one of renal failure and uremia, and there are marked degenerative changes in the kidneys as well as the liver. In both groups death is too late for shock, and there is no sign of infection at autopsy. Boyce and McFetridge have reproduced the syndrome in rabbits by first obstructing the biliary tree and then suddenly releasing the obstruction, and also by producing subcapsular trauma to the liver. They suggest the sudden death with hyperpyrexia and what may be called the *hepato-renal syndrome* are successive stages of the same pathological process. It may be that the liver is damaged to some degree in biliary tract disease and its detoxifying power interfered with. The various injurious factors inseparable from an abdominal operation and the sudden release of obstruction may intensify this damage, as a result of which the circulation is flooded with toxins, some of which may be due to direct damage to liver tissue. These toxins, when not powerful enough to produce early death, may injure the renal epithelium and cause death from renal failure.

#### ADDITIONAL READING

- Agonal Changes.** POPPER: Arch. Path., 1948, 46, 132.  
**Alcoholic Cirrhosis.** CONNOR: Am. J. Path., 1938, 14, 347. HALL AND MORGAN: Arch. Path., 1939, 27, 672.  
**Carcinoma of Liver.** COPELAND AND SALMON: Am. J. Path., 1946, 22, 1059. ORSÓS: Beitr. z. path. Anat. u. z. allg. Path., 1930, 84, 33. SASAKI AND YOSHIDA: Virchows Arch. f. path. Anat., 1935, 295, 175. STRONG AND PITTS: Arch. Int. Med., 1930, 46, 105. SUGIURA AND RHOADS: Cancer Research, 1941, 1, 3. TULL: J. Path. and Bact., 1932, 35, 557. WILBUR, *et al.*: Ann. Int. Med., 1944, 20, 453.  
**Cholecystitis.** ANDREWS: Arch. Surg., 1935, 31, 767. NEWMAN: Lancet, 1933, 1, 841, 896. WESTPHAL, *et al.*: Gallenwegsfunktion und Gallensteinleiden, Berlin, 1931. WILKIE: Brit. J. Surg., 1928, 15, 450. WOMACK AND BRICKER: Proc. Soc. Exper. Biol. and Med., 1940, 45, 710.  
**Cholesterosis of Gall-bladder.** BOYD: Brit. J. Surg., 1923, 10, 337. ELMAN AND GRAHAM: Arch. Surg., 1932, 24, 14. ILLINGWORTH: Brit. J. Surg., 1929, 17, 203.  
**Cinchophen Poisoning.** PERMAR: Arch. Int. Med., 1933, 52, 398.  
**Cirrhosis of Liver.** HARTROFT: Anat. Rec., 1950, 106, 61. HARTROFT AND RIDOUT: Am. J. Path., 1951, 27, 951. KARSNER: Am. J. Clin. Path., 1943, 13, 569.  
**Diverticula of Gall-bladder.** ROBERTSON AND FERGUSON: Arch. Path., 1945, 40, 312.  
**Eclampsia.** DILL AND ERICKSON: Arch. Path., 1941, 31, 68.  
**Elastosis of Gall-bladder.** RIOPELLE: Arch. Path., 1949, 48, 55.  
**Fatty Liver.**—BEST AND CAMPBELL: J. Physiol., 1936, 86, 190.  
**Gall Stones.** ANDREWS, *et al.*: Arch. Surg., 1932, 25, 796. ASCHOFF: Lectures in Pathology, New York, 1924.  
**Glycogen Accumulation.** VON GIERKE: Beitr. z. path. Anat. u. z. allg. Path., 1929, 82, 497. WORSTER-DROUGHT: Brit. Med. J., 1933, 1, 403.  
**Glycogen in Liver Cells.** CHIPPS AND DUFF: Am. J. Path., 1942, 18, 645. MORRIONE AND MAMELOK: Am. J. Path., 1952, 28, 497.  
**Hemolytic Jaundice.** FÄHRÆUS: Lancet, 1939, 2, 630.  
**Infarct of Liver.** CAMERON AND MAYES: J. Path. and Bact., 1930, 33, 799. LUND, *et al.*: Am. J. Path., 1935, 11, 157. PASS: Am. J. Path., 1935, 11, 503.

- Infectious Hepatitis.** CAMERON: Quart. J. Med., 1943, 12, 139. DIBLE, *et al.*: Lancet, 1943, 2, 402. LUCKÉ: Am. J. Path., 1944, 20, 471, 595. LUCKÉ AND MALLORY: Am. J. Path., 1946, 22, 867. NEEFE AND STOKES: J. A. M. A., 1945, 128, 1063. ROHOLM AND IVERSEN: Acta path. et microbiol. Scand. Scand., 1939, 16, 427. WOOD: Arch. Path., 1946, 41, 345.
- Infectious Hepatitis and Cirrhosis.** MACMAHON: Am. J. Path., 1931, 7, 77. MACMAHON AND MALLORY: Am. J. Path., 1931, 7, 299. MOON: Arch. Path., 1932, 13, 691.
- Jaundice.** BARBER AND OSBORN: J. Path. and Bact., 1939, 49, 581. KLEMPERER, *et al.*: Arch. Path., 1926, 2, 631. RICH: Bull. Johns Hopkins Hosp., 1930, 47, 358; Physiol. Rev., 1925, 5, 182.
- Laennec's Cirrhosis.** RATNOFF AND PATEK: Medicine, 1942, 21, 207.
- Liver Death.** BOYCE AND MCFETRIDGE: Arch. Surg., 1935, 31, 105. HEYD: J. A. M. A., 1931, 97, 1847.
- Obstructive Biliary Cirrhosis.** MACMAHON AND MALLORY: Am. J. Path., 1929, 5, 645.
- Pigment Cirrhosis.** MALLORY AND PARKER: Am. J. Path., 1931, 7, 351 and 365.
- Portal Cirrhosis.** BENNETT, *et al.*: Am. J. Clin. Path., 1950, 20, 814. CAMERON AND KARUNARATNE: J. Path. and Bact., 1936, 42, 1. CHAIKOFF, *et al.*: Am. J. Path., 1943, 19, 9. CONNOR: Am. J. Path., 1938, 14, 347; J. A. M. A., 1939, 112, 387. GLYNN AND HIMSWORTH: J. Path. and Bact., 1944, 56, 297. HIMSWORTH AND GLYNN: Lancet, 1944, 1, 457. MORRIONE: Arch. Path., 1944, 37, 39. STEINBERG AND MARTIN: Arch. Path., 1946, 41, 1.
- Primary Tumors of Liver.** WARVI: Arch. Path., 1944, 37, 367.
- Sudden Death in Fatty Liver.** GRAHAM: Bull. Johns Hopkins Hosp., 1944, 74, 16. LE COUNT AND SINGER: Arch. Path., 1926, 1, 84.
- Viral and Toxic Hepatitis.** POPPER AND FRANKLIN: Arch. Path., 1948, 46, 338.
- Weil's Disease.** ASHE, *et al.*: Medicine, 1941, 20, 145. JEGHERS, *et al.*: Arch. Path., 1935, 20, 447.

## THE PANCREAS

THE pancreas is in reality a double organ. It is an acinar digestive gland secreting the most powerful of all the digestive juices. For this reason postmortem changes occur very quickly, and the finer forms of investigation, such as an examination of the islet tissue for the specific A and B granules, should be carried out as soon after death as possible. It is also one of the endocrine glands, for the islets of Langerhans form one of the chief regulators of carbohydrate metabolism. The pathology of the pancreas therefore assumes a twofold aspect.

## PANCREATITIS

**Acute Hemorrhagic Pancreatitis.**—This is really a pancreatic necrosis to which hemorrhage may or may not be added. A preferable name would therefore be *acute pancreatic necrosis*. This is one of the acute abdominal catastrophies. The pain comes on suddenly, after a large meal, and is even more agonizing than that of perforated gastric ulcer. The patient lies perfectly motionless, not tossing about as in renal or biliary colic, passes into a condition of shock, and shows a peculiar and characteristic slaty-blue cyanosis. There is marked increase in the serum amylase.

**ETIOLOGY.**—The cause of the condition is a matter of perennial dispute. The acute necrosis is due to the action of the pancreatic enzymes liberated from the ducts. The problem is to explain how they escape. The usual view is that it is due to the passage of infected bile along the pancreatic duct; this activates the trypsinogen in the pancreas and converts it into trypsin, which proceeds to digest the pancreas. More than one-half the cases are associated with cholecystitis or calculi. Opie originally pointed out that if the common bile duct and pancreatic duct open into a common chamber (as occurs in 70 per cent of persons), impaction of a calculus at the ampulla of Vater will cause the bile to flow into the pancreas. This is a possible but very uncommon cause. Archibald has shown that in the cat spasm of the muscle of Oddi at the ampulla of Vater is followed by a flow of bile into the pancreas, and such spasm may be produced by pressure on the gall-bladder or by painting the ampulla with weak hydrochloric acid. This is a probable cause in many cases. The matter cannot be regarded as settled, for Mann has pointed out that in the human subject the sphincter is usually not placed distal to the entry of both ducts, but proximal to the termination of the bile duct, and he suggests that here clinical imagination has preceded the demonstrated facts.

Rich and Duff have suggested a different explanation. They found that in both human and experimental hemorrhagic pancreatitis the constant and specific lesion was rapid necrosis of the walls of the arteries and veins, hemorrhage being due to rupture of the necrotic walls. Moreover, they found that the pancreatic juice was able to produce necrosis without activation of the trypsinogen by intestinal contents or bile. They believe that the mechanism involved is rupture of dilated thinned-out acini behind an obstructed duct, this rupture being liable to occur from increased pressure in the ducts due to marked secretion after a large meal. The main duct may be obstructed by a gall stone at the ampulla, but they found that the obstruction was usually in one of the smaller branches, being caused by squamous metaplasia and piling up of the lining epithelium (Fig. 299).



FIG. 299.—Squamous metaplasia in pancreatic duct.  $\times 240$ .

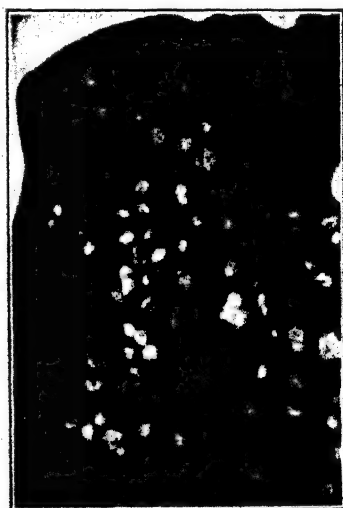


FIG. 300.—Fat necrosis of pancreas.

This lesion was present in over half the cases of hemorrhagic pancreatitis. On the other hand Baggenstoss found only one example of squamous metaplasia of the ducts in 29 cases of chronic relapsing pancreatitis considered to be due to repeated attacks of acute pancreatitis. The probable truth is that all of the factors outlined above may at times be responsible for producing the condition.

The *cause of death* is probably the poisonous split-protein products formed as the result of partial digestion of the pancreatic tissue. These products are absorbed very quickly, and this, together with the profound degree of shock, perhaps accounts for the extraordinarily rapid termination of many of the cases.



**LESIONS.**—The pancreas is swollen, soft, and dark in color. It may be red from hemorrhage or black and gangrenous. Hemorrhage is an accidental occurrence, which may or may not be present. Sometimes it dominates the picture. A pancreas may appear normal to the naked eye and yet may show the characteristic necrosis microscopically. The marked swelling is probably responsible for much of the severe pain. Small necrotic areas may be replaced by fibrous tissue. Larger areas may be infected and form abscesses. The greater part of the pancreas may be destroyed. The peritoneal cavity contains a characteristic fluid, dirty, fatty, and beef-juice in character. The *microscopic appearance* is one of great necrosis of the acinar tissue, so that in the advanced cases no structure can be made out. A varying degree of hemorrhage takes place into this necrotic tissue.

*Fat necrosis* is often seen in acute pancreatitis and is pathognomonic of that condition when encountered at operation. Small, dull, opaque white areas are scattered over the surface of the pancreas and the surrounding omentum and mesentery (Fig. 300). These represent areas of fat which have been broken down by the lipase in the liberated pancreatic juice. Areas of fat necrosis may be found at some distance from the pancreas and even in the thorax, owing to distribution of the lipase by the lymphatics. Glycerol and fatty acids are formed; the glycerol is absorbed, and the fatty acids are deposited in the cell as acicular crystals. The areas tend to be absorbed in the course of a few weeks, but the fatty acids may unite with calcium, so that some of the patches may become calcified. *Microscopically* the necrosed cells have an opaque appearance, in comparison with the clear cells of normal fat which is all dissolved out by the chloroform or xylol used for clearing the tissue. One part of a fat globule may show this opaque appearance while the rest of it is clear (Fig. 16, page 44). The necrotic area is usually surrounded by a zone of leucocytes. Associated with acute pancreatitis at autopsy there may be myocardial infarction or profound fatty change in the liver due to chronic alcoholism. Whether this association is by chance or has a basis in causality it is not possible to say.

**CHRONIC PANCREATITIS.**—In this condition the pancreas is hard and sclerotic, and there is marked atrophy of the parenchyma and increase of the fibrous stroma. The most probable cause is the repeated entry of mildly infected bile into the pancreatic duct, but of this it is impossible to be certain. As the islets of Langerhans do not belong to the acinar system they are usually spared, but if the sclerosis is severe the islets are injured, and diabetes is then present. On account of the hardness the condition is easily mistaken by the surgeon for carcinoma of the head of the pancreas.

## DIABETES MELLITUS

**ETIOLOGY.**—The cause of diabetes is unknown. The disease usually begins after middle life, but is more severe in the young. Obesity seems to be a predisposing factor. The essence of the condition appears to be a disturbance of the normal balance of the factors regulating carbohydrate metabolism. In this regulation the liver plays the most important part, but the hormonal output of the pancreas, pituitary and adrenals is also essential. In all cases of diabetes there is an insufficiency of insulin in

relation to the needs of the organism, but the actual secretion may be normal or increased. In other words, it is not necessarily a disease of the pancreas. Indeed pancreatectomy may actually relieve diabetes, and persons with total pancreatectomy may require less insulin than do many diabetics. In one of my cases not only were the islets apparently normal, but there was also an adenoma of the islets. The pituitary, thyroid and adrenals have an action antagonistic to that of the pancreas.

Excision of the pituitary relieves the experimental diabetes produced by removal of the pancreas (Houssay). Conversely it has been shown that permanent diabetes can be caused by repeated injections of extract of the anterior pituitary (Young), perhaps due to initial stimulation and subsequent exhaustion of the islets. In the early stages there is disappearance



FIG. 301.—Islet of Langerhans in experimental diabetes showing extreme hydropic degeneration of the Beta cells.  $\times 500$ . (From a preparation by Dr. D. J. Bowie.)

of the granules in the Beta cells, hydropic degeneration of these cells, and marked cellular proliferation as indicated by numerous mitoses. The later changes are hyalinization with final complete disappearance of the islets. Similar exhaustive changes are seen in experimental diabetes produced by excision of nine-tenths of the pancreas followed by a carbohydrate diet. In the remaining portion of the pancreas the exhausted Beta cells show loss of the specific granules and marked hydropic degeneration (Fig. 301); finally they rupture or degenerate and disappear.

Selective necrosis of the islets can be produced by the intravenous injection of alloxan, one of the components of uric acid. Alloxan destroys all the Beta cells in a dog in the course of two days. They simply vanish. Their place is taken by Alpha cells which become greatly enlarged, so that in a hematoxylin and eosin section the islets may appear normal. Special granule stains such as that of Gomori tell the true story. The *alloxan diabetes* which results is characterized by a marked and fatal hypoglycemia, which is preceded by a puzzling transient hyperglycemia. There are thus three ways of producing diabetes experimentally: (1) by pancreatectomy, (2) by injection of anterior pituitary extract, (3) by injection of alloxan.

**SYMPTOMS.**—Glycosuria is the chief symptom of diabetes (*mellitus*, sweetened with honey), associated with polyuria (*diabetes*, a syphon or running through), excessive thirst and hunger, and marked loss of weight. Another group of symptoms due to incomplete combustion of fats are manifestations of acidosis, *e.g.*, air hunger, coma, ketone bodies in the urine, and lipemia. Pruritus, carotinemia, gall stones, arteriosclerosis, and gangrene of the extremities may occur. Neuritis is an unexplained accompaniment of many cases of diabetes. It bears some relation to the level of the blood sugar.

**LESIONS.**—Although the patient may have died of diabetes, the pancreas generally appears normal to the naked eye, because the acinar tissue is unaffected. With hematoxylin and eosin staining the microscopic picture may also be disappointing.



FIG. 302.—Loss of Beta granules in diabetes.  $\times 470$ .

The islets may be greatly diminished in number, but they may be normally abundant and even hypertrophied. When granule stains are used, of which the best is that of Gomori, it is seen that the basic lesion is the disappearance of the granules in the Beta cells (Fig. 302). If these cells are replaced by hypertrophied Alpha cells, the islets may seem to be normal. In very acute cases in children hydropic degeneration of the Beta cells may be detected. Hyaline degeneration of the islets is often seen (Fig. 303), but it is also common in persons over middle age, *i.e.*, the diabetic period. Many diabetics do not die directly of diabetes but of such complications as arteriosclerosis, renal failure and gangrene. In such persons under insulin therapy the islets are no longer under strain and may have undergone regeneration. Finally it must be remembered that diabetes is the result of a disturbance of the normal balance of the factors

regulating carbohydrate metabolism, and that in some cases the pancreas may not be the chief offender.

It may well be that some of the characteristic lesions of diabetes may be manifestations of a disturbance of metabolism of a simple polysaccharide (glycogen) or of the more complex mucopolysaccharides. The hydropic change in the islets is due in part to a deposition of glycogen (Toreson), and the hyaline of the islets gives the staining reaction for mucopolysaccharides. The same is true of the Kimmelstiel-Wilson lesions. Even the arteriosclerotic lesions may be preceded by a change in the mucopolysaccharide of the ground substance of the vessel wall.

**LESIONS OUTSIDE THE PANCREAS.**—The diabetic under modern treatment is not likely to die of diabetic coma. He lives for many years and then dies from what are called complications, but are really late manifestations

## PLATE XV



Glycogen in Renal Tubules

From a case of diabetes mellitus. Stained with Best's carmine.

of the upset in metabolism which is the essence of the disease. The late lesions are vascular, retinal and renal.

*Vascular lesions* are of all varieties of arteriosclerosis. They result in gangrene, coronary artery disease and apoplexy. Hypertension is a good deal commoner in diabetics than in non-diabetics, bringing its own vascular troubles. The elderly diabetic is threatened with gangrene, coronary disease and cerebral hemorrhage.

*Diabetic retinopathy* develops especially in juvenile diabetics who have had the disease for upward of fifteen years. In those who have had the disease for twenty years it is present in 90 per cent of cases. The red spots



FIG. 303.—Pancreas in diabetes. The islet of Langerhans shows an extreme degree of hyaline degeneration.  $\times 325$ .



FIG. 304.—The kidney in diabetes. The clear cells of the loop of Henle are filled with glycogen.  $\times 200$ .

seen with the ophthalmoscope, which used to be taken for punctate hemorrhages, are now known to be globular microaneurisms of capillaries in the inner molecular layer of the retina. They are present in great numbers, and they may be the source of hemorrhage and thrombosis. To the physician who sees them they are an ominous sign.

The *renal lesions* are of great importance, for the danger of death from diabetic coma has been replaced by the danger of death from renal failure. The younger the age of onset of the diabetes the shorter is the duration needed for the development of renal lesions. There are five principal lesions: glycogen in the renal tubules, arteriosclerosis, the Kimmelstiel-Wilson lesion, pyelonephritis, and papillitis necroticans. The most characteristic renal lesion used to be an accumulation of glycogen in the tubules, giving the cells a clear, transparent appearance (Fig. 304). The chief deposits are in the loop of Henle (Plate XV). Glycogen is seldom seen now owing to adequate treatment with insulin. *Renal arteriosclerosis* is common

and severe in juvenile diabetics who have had the disease for fifteen years or more, particularly in females. It is likely to cause death from renal failure. The *Kimmelstiel-Wilson lesion* or intercapillary glomerulosclerosis when present in typical form is pathognomonic of diabetes. It is described on page 564. *Pyelonephritis* is again commoner in the female in the proportion of 2 to 1. In my own autopsy material more patients appeared to die from pyelonephritis than from any other renal lesion. *Papillitis necroticans* is the rarest of the lesions in my experience. It occurs in association with acute pyelonephritis, and pursues a fast and fatal course. The necrosis of one or more of the renal papillae seems to be due to vascular occlusion. The lesion is described on page 585.

*Lipemia* may be marked. When the blood fat is high the plasma may be milky. In exceptional cases there is a remarkable *lipid storage* in the cells of the reticulo-endothelial system. The cells become swollen with lipid which may take the form of globules. These large "foam cells" are seen in the spleen and liver (Kupffer cells). The lipid is usually cholesterol ester. There may be yellow patches in the aorta and yellow nodules in the skin (*xanthoma diabeticum*), which are deposits of the same material. The yellow color of the skin (*xanthosis*) sometimes seen in diabetics is not due to lipemia but to carotin, a pigment contained in carrots and other vegetables. There is a carotinemia, and the serum is bright yellow. The coloration of the skin is best seen in the nasolabial folds and on the palms of the hands and soles of the feet.

It is an interesting fact that neonatal mortality and also the average birth weight are increased among infants born to mothers who subsequently develop diabetes. Infants born to diabetic mothers have a still higher fetal and neonatal mortality rate.

*Fibrocystic Disease.*—The condition originally known as cystic fibrosis of the pancreas (Anderson) is now recognized to be a systemic disease of childhood with a variety of clinical appearances, the occurrence of which depends on the time at which the lesions occur and on which organs are affected (Farber). It is a generalized disorder, characterized by the secretion of abnormal mucus, a mucosis, which is genetically determined and may appropriately be included with the inborn errors of metabolism. The most striking lesions occur in the pancreas. Usually that organ is firmer and thinner than normal, but it may show no gross change or may be nodular. The acinar tissue is atrophied and replaced by fibrous tissue. The small and large ducts are dilated and filled with homogeneous eosinophilic material like inspissated secretion, and the acini may contain similar material (Fig. 305). Baggenstoss has examined the pancreas in a number of cases by serial microscopic sections, and in every case has found atresia either of the main ducts or of the interlobular ducts. The mucous glands of the trachea and bronchi are also filled with inspissated material, and a similar condition prevails in the salivary glands, duodenum, jejunum, and gall-bladder. The dilatation of the pancreatic ducts may lead to cyst formation. The obstructive lesions of the pancreas may result in two quite dissimilar pictures in infancy and childhood, depending on the time of onset of the lesions. If pancreatic achylia occurs during the latter part of intrauterine life the result is an inspissated meconium which may cause intestinal obstruction shortly after birth (meconium ileus). If the achylia does not develop for a few weeks after birth the clinical picture is one of severe nutritional deficiency closely resembling celiac disease. Respiratory symptoms may dominate the

picture; these are due to obstruction of the bronchi and bronchioles by thick tenacious mucus, which eventually leads to bronchiectasis. A marked degree of squamous metaplasia may be associated with the bronchiectasis, but the relationship of one to the other is obscure.

In one of my cases, a boy seventeen years of age in whom this metaplasia reached an extreme degree, there was marked coarsely nodular cirrhosis of the liver. In this case the acinar tissue of the pancreas was entirely replaced not by fibrous tissue but by fat. Some of the symptoms seem to be due to defective absorption of vitamin A, but it is a mistake to attribute the fundamental lesions to a congenital deficiency of this vitamin. Farber points out that the widespread involvement of mucus-secreting structures suggests a possible deficiency of the mucinase required for the maintenance of mucus in a normal physical state.

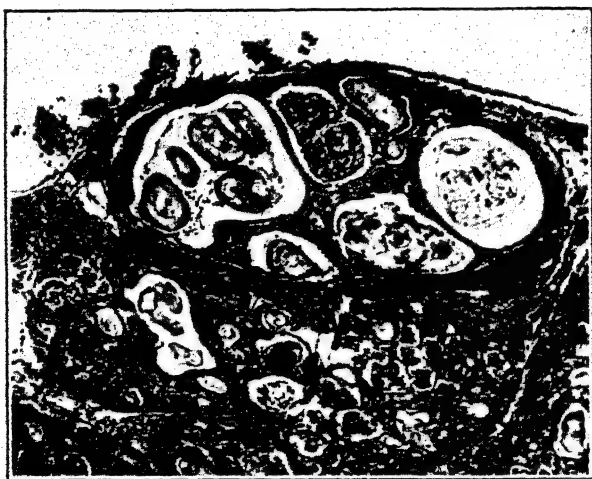


FIG. 305.—Fibrocystic disease of the pancreas.

**OTHER PANCREATIC CYSTS.**—These may be congenital cysts, cystadenomas, or pseudocysts. *Congenital cysts* are rare, and are part of congenital cystic disease involving the kidneys and sometimes the liver. *Cystadenomas* are rare tumors which may be benign or malignant. *Pseudocysts* are the common variety, but they are not true cysts of the pancreas and have no epithelial lining. They are usually situated in front of the pancreas in the lesser sac of peritoneum. They may attain a large size. The cyst is preceded by some injury to the pancreas, either trauma or acute hemorrhagic pancreatitis, as a result of which the pancreatic secretion escapes into the lesser sac, and as the foramen of Winslow becomes sealed a cyst develops. The fluid may be clear and serous, or yellow or brown from hemorrhage. The fluid may contain pancreatic ferments, but their absence does not mean that the cyst is not of this nature, for they often disappear.

### CALCULI OF THE PANCREAS

These small stones in the pancreatic duct are rare. They consist of calcium and phosphate. They may cause obstruction or bacterial infection.

## TUMORS OF THE PANCREAS

**Carcinoma.**—This is the common tumor of the pancreas. Like other cancers of the digestive tract, it is much commoner in men than in women. At least 70 per cent of the cases occur in the head of the pancreas (Fig. 306). This part of the gland is enlarged and remarkably hard. The hardness may simulate chronic pancreatitis, and the surgeon may find it difficult or even impossible to distinguish between the two conditions at an exploratory laparotomy. *Microscopically* the tumor may arise from the ducts or the acini. The duct tumor, which is far the commoner, is an adenocarcinoma; the columnar cells have clearly defined margins, a vesicular nucleus and a distinct nucleolus. In the acinar cell type there are lobular masses of polyhedral or rounded cells, with poorly defined cell

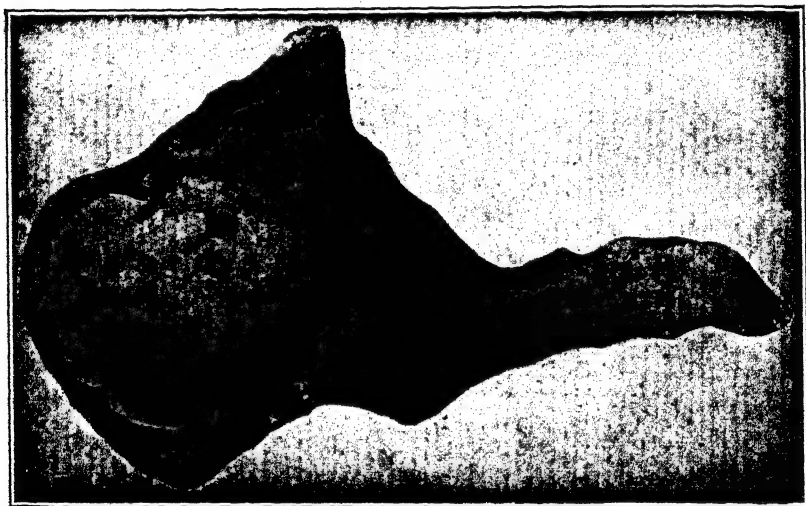


FIG. 306.—Carcinoma of the head of the pancreas causing marked displacement of the second part of the duodenum.

margins, large hyperchromatic nuclei, and no visible nucleoli. Secondary growths occur in the regional lymph nodes and liver. The symptoms depend on the location of the tumor. In cancer of the head of the pancreas the chief symptom is persistent and increasing jaundice, due to pressure on the opening of the common bile duct. The bladder is dilated and thin-walled in accordance with Courvoisier's law. In cancer of the body and tail spread is a more striking feature, and this influences the symptoms (Duff). Deep-seated gnawing pain is due to spread along the perineural lymphatics, ascites is caused by implantation growths on the peritoneum or involvement of the portal vein, and distant metastases are more common than in cancer of the head.



*Secondary carcinoma* is not common in the pancreas. There may be invasion from the stomach, gall-bladder or bile duct. In rare cases there may be metastases from hypernephroma and other tumors.

*Adenoma*.—These tumors are rarely seen, but Warren suggests that this is because they are so small that they are overlooked at autopsy. They are composed of acinar tissue and are definitely encapsulated.

**Tumors of the Islets of Langerhans.**—This is an uncommon but very interesting group. The tumor is usually benign (adenoma), but cases of carcinoma have been reported. The adenoma can easily be removed surgically, with dramatic results. A simple way to distinguish between tumor cells and acinar cells is to stain the zymogen granules of the latter; this is much easier than to stain the specific granules of the islet cells. It has been suggested that these lesions are in the nature of heterotopia rather than adenoma; this would serve to explain the occasional presence of duct-like structures, absence of encapsulation and apparently invasive growth (Holmes *et al.*). Sometimes there is a diffuse hypertrophy of the islet tissue throughout the pancreas rather than a localized adenoma. These cases naturally do not lend themselves to operation. The *symptoms* are those of hyperinsulinism or insulin shock with marked hypoglycemia due to overactivity of the islet tissue and overproduction of insulin. There may be attacks of faintness and unconsciousness when the interval after a meal is too long, and these can be averted by taking sugar. The condition is therefore the reverse of diabetes.

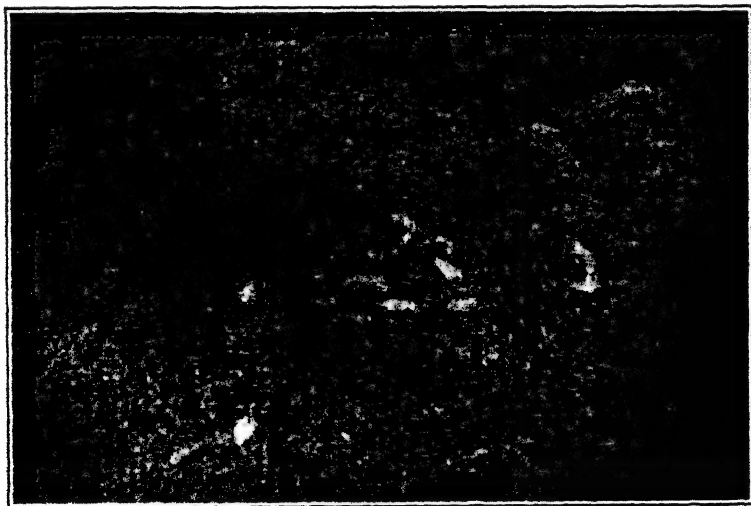


FIG. 307.—Almost complete disappearance of acini due to obstruction of the pancreatic duct. The islets remain intact.  $\times 150$ .

### OBSTRUCTION OF THE PANCREATIC DUCT

Obstruction may be caused by cancer of the head of the pancreas, a gall stone impacted at the ampulla of Vater, a pancreatic calculus, or cicatricial

contraction. The ducts become irregularly dilated, the acini atrophy and disappear and are replaced by fibrous tissue. The islets of Langerhans are unaffected, and as the pancreas shrinks in bulk, these structures appear to be more numerous and stand out with great distinctness. It was by producing experimental obstruction of the pancreatic duct by means of ligature that Banting and Best first succeeded in freeing the islet tissue from the tripsinogen-producing acini and were thus enabled to extract insulin. Carcinoma of the head of the pancreas may occasionally produce exactly the same effect (Fig. 307).

### HEMOCHROMATOSIS (BRONZED DIABETES)

This rare condition has already been considered in Chapter 2. It is a disorder of iron metabolism characterized by the most extreme hemosiderosis. The pancreas is of a rich brown color. Both the acinar tissue and the islets are loaded with granules of hemosiderin, so that they give an intense Prussian blue reaction. A slow process of necrosis occurs in the damaged cells, and gradually they atrophy, disappear, and are replaced by fibrous tissue. As the islets are destroyed as well as the acinar tissue, diabetes develops.

### OTHER LESIONS OF THE PANCREAS

**LIPOMATOSIS.**—This is merely a local manifestation of obesity. Large fat cells occupy the interstitial tissue, and if the lipomatosis is extreme it may cause some atrophy of the acinar tissue.

**CONGENITAL ANOMALIES.**—Malformations of various kinds may occur. The best defined of these is the condition known as *annular* or *ring pancreas*, in which the head of the pancreas surrounds the second part of the duodenum and may cause some constriction. Of more importance is *heterotopia of the pancreas*, a condition in which accessory pancreatic tissue is found in the pyloric end of the stomach, the duodenum, and more rarely in the ileum and even the mesentery.

### ADDITIONAL READING

- Acute Pancreatitis.** MANN AND GIORDANO: Arch. Surg., 1923, 6, 1. MYNIHAN: Ann. Surg., 1925, 81, 132. RICH AND DUFF: Bull. Johns Hopkins Hosp., 1936, 58, 212.
- Alloxan Diabetes.** DUNN, *et al.*: J. Path. and Bact., 1943, 55, 245.
- Carcinoma of Pancreas.** DUFF: Bull. Johns Hopkins Hosp., 1939, 65, 69.
- Chronic Pancreatitis.** BAGGENSTOSS: Proc. Staff Meetings, Mayo Clinic, 1947, 22, 542.
- Diabetes Mellitus.** EDMONDSON, *et al.*: Arch. Int. Med., 1947, 79, 148. HOUSSAY: Am. J. Med. Sci., 1937, 193, 581. WARREN: The Pathology of Diabetes Mellitus, 3rd ed., Philadelphia, 1952.
- Experimental Diabetes.** DUFF: Am. J. Med. Sci., 1945, 210, 381.
- Fibrocystic Disease of Pancreas.** ANDERSON: Am. J. Dis. Child., 1938, 56, 344. BAGGENSTOSS, *et al.*: Arch. Path., 1951, 51, 510. BODIAN: Fibrocystic Disease of the Pancreas, London, 1953. FARBER: Arch. Path., 1944, 37, 238; New England J. Med., 1943, 229, 653. WARREN AND Lecompte: The Pathology of Diabetes Mellitus, 3rd ed., Philadelphia, 1952.
- Hydropic Degeneration.** TORENSEN: Am. J. Path., 1951, 27, 327.
- Islet Cell Tumors.** DUFF: Am. J. Med. Sci., 1942, 203, 437. HOLMES, *et al.*: Brit. J. Surg., 1946, 33, 330. LAIDLAW: Am. J. Path., 1938, 14, 125.

## THE PERITONEUM AND ABDOMINAL WALL

## ACUTE PERITONITIS

**ETIOLOGY.**—Acute inflammation of the peritoneum is the result of bacterial infection, although a local reaction may be caused by such aseptic irritants as a strip of gauze or a drainage tube, and a more general reaction by hemorrhage or the escape of fluid from a cyst. The common bacteria found are *Bacillus coli* and streptococci; less frequent are staphylococcus, pneumococcus, gonococcus, *Bacillus pyocyaneus*, *Bacillus typhosus*, and certain anaerobic bacilli. The most acute and diffuse cases are those due to streptococci.

The infection may reach the peritoneum in three ways: (1) *From an abdominal organ.* This is much the commonest way, and the usual source is the gastro-intestinal canal. Appendicitis easily heads the list, followed by gastric, typhoid, and dysentery ulcers, ulcerating carcinoma, etc. When the bowel becomes strangulated (hernia, etc.) or when it is gangrenous from infarction, peritonitis quickly develops. When the infection comes from the hollow viscera there may either be perforation with an outpouring of intestinal contents (ruptured appendix, perforated gastric ulcer), or the bacteria may pass through the intact but inflamed wall of the bowel. It is evident that in the former case the resulting peritonitis is more likely to be widespread and overwhelming. The female pelvic organs form a second important group, of which the principal members are puerperal sepsis, which is nearly always streptococcal, and gonococcal infection of the Fallopian tubes, which usually causes a local inflammation limited by adhesions. Other occasional sources of infection are acute cholecystitis, hemorrhagic pancreatitis, abscess of the liver, etc. (2) *From the exterior.* This may be due to an accident, or may occur in the course of a surgical operation. (3) *Hematogenous* infection is very rare; it is seen in the secondary form of pneumococcal peritonitis.

General peritonitis used to be a much dreaded and commonly fatal condition. The introduction of chemotherapy has profoundly changed the outlook.

**MORBID ANATOMY.**—Peritonitis is at first a local condition. It may remain local or may become diffuse. At first the membrane merely appears pink and injected. Then the normal sheen is lost and replaced by a frosted appearance, due to the formation of a layer of fibrin on the surface. Finally the coils of bowel are glued together by a sticky exudate. Meanwhile a fluid exudate is being formed, and collects especially between the adherent coils of bowel. At first it is serous, but soon it becomes purulent. A thick creamy exudate is a better sign than a thin seropurulent one, which always suggests severe streptococcal infection with low resistance and a bad prognosis. Hemorrhagic fluid is seen in infarction of the bowel, strangulations, etc. The *microscopic appearance* is that of an inflamed serous membrane. The chief element of the exudate in the early stages is fibrin, but if the condition becomes purulent there may be a thick layer of polymorpho-

nuclear leucocytes together with a variable number of red blood cells. The surface endothelium may be desquamated, but even in severe cases it sometimes remains intact under the exudate.

**SPREAD.**—Spread may occur over the surface or *via* the lymphatics. *Surface spread* tends to be limited by protective adhesions, and by the action of the great omentum, which plays the part of the abdominal policeman, spreading itself over the inflamed area, sealing up a threatened perforation, and generally acting the part of guardian to the hollow viscera. It effectively prevents many a case of local peritonitis from becoming general. When the omentum is found in an abnormal position and adhering to a viscus, it is safe to assume that trouble is brewing. *Lymph spread* takes place with great rapidity in the subserous lymphatics in streptococcal infections, much as the infection spreads in erysipelas.

The great *danger* of general peritonitis is *paralytic ileus* rather than septicemia, for inflammation tends to seal the channels of absorption. If a coil of ileum hangs down so as to dip into a pool of pus in the pelvis it will become paralyzed and be as completely obstructed as if a ligature had been tied around it. The proximal part of the small bowel becomes acutely dilated and its lumen is soon filled with highly toxic material. Symptoms of acute intestinal obstruction with toxic absorption are now added to the picture, but are apt to be obscured and overlooked with fatal consequences. The surgeon cannot attack and drain a generally infected peritoneal cavity, but he can relieve the distended small bowel by inserting a tube. It has been well said that "if the bowels can be made to act, the patient recovers; if they fail to act, he dies."

The *end-results* are complete recovery, the formation of fibrous adhesions, or death. The question of adhesions is considered later. They are not always permanent and may sometimes disappear.

**Varieties of Peritonitis.**—The pyogenic microorganisms responsible for acute peritonitis give rise to lesions which have many features in common, but some of the types may be considered separately.

**PNEUMOCOCCAL PERITONITIS.**—This variety is in a class by itself and should be separated in the mind from the other forms of acute peritonitis. It may be *secondary* to a primary focus elsewhere, usually in the lung or middle ear. The mode of infection is either by the blood stream or through the diaphragm.

The *primary form* occurs principally in childhood, but I have seen a case in a woman aged sixty-two years. McCartney and Fraser, in a study of 56 cases, did not find a single example in a boy. It is a disease of the poorer classes, and is probably due to lack of cleanliness. McCartney and Fraser have shown that infection may occur by way of the female genital tract, thus explaining the peculiar sex incidence. The statistics of the Hospital for Sick Children, Toronto, provide an interesting contrast to those which have just been quoted. Of 39 cases of proved primary pneumococcal peritonitis, 30 were females and 9 were males. The usual age incidence is between the third and seventh years.

The disease begins as a pelvic peritonitis but the infection rapidly spreads. The fimbriae of the tubes are congested and pus containing pneumococci can be expressed. The exudate is at first watery, containing flakes of fibrin. It is only later that it becomes purulent.

**GONOCOCCAL PERITONITIS.**—Gonococcal peritonitis is a disease of the female, the infection passing along the Fallopian tube. In rare cases it may follow infection

of the seminal vesicles in the male. The peritonitis usually remains confined to the pelvis, and after a short acute phase soon becomes chronic, but occasionally the inflammation may be general. Its chief characteristic is the formation of very dense fibrous adhesions in the pelvis.

**LOCALIZED PERITONITIS.**—It is not usual for inflammation of the peritoneum to become generalized. Unless the infection is overwhelming, as in perforation of a hollow viscus or gangrene of the bowel which allows ready passage of enormous numbers of bacteria, there is a tendency for the process to be localized. Two things may happen. (1) The inflammation may pass off and the membrane return to a normal state, or there may be thickening and adhesions. (2) Pus may be formed, which is limited by adhesions to form an abscess such as the periappendicular abscess which follows acute appendicitis. It is unusual for such an abscess to open into the peritoneal cavity; it is more likely to discharge onto the skin surface or into a hollow viscus. These localized peritoneal abscesses are often seen in the female pelvis. A special form is the subdiaphragmatic or subphrenic abscess.

A *subphrenic abscess* is a collection of pus between the diaphragm above, and the liver, stomach, or spleen below. In most of the cases the original inflammatory focus is in the upper part of the abdomen, especially gastric and duodenal ulcer and abscess of the liver, but the pus may trek up from below, *e.g.*, appendicular abscess, pelvic abscess. The site of the initial focus of infection determines whether the abscess be under the right dome of the diaphragm or the left. The abscess is shut off from the general abdominal cavity by adhesions. Usually the pus is intraperitoneal, but when the primary lesion is in the appendix, liver, or kidney, the pus is retroperitoneal. The diaphragm is pushed up on the affected side as shown by the roentgen-rays and the liver is pushed down. The condition is progressive, and the abscess may burst into the peritoneal, pleural, or pericardial cavities.

**LYCOPodium PERITONITIS.**—*Lycopodium* spores which used to be a constituent of the dusting powder of surgical gloves may cause a localized peritonitis with the formation of adhesions or large numbers of small surface nodules which may be mistaken for tubercles or carcinomatosis. The surface of the spore (the edge as seen in a section) is furnished with firm spicules which cause it to adhere to any surface with which it comes in contact, and to be forced beneath that surface by any manipulation. The lesions consist of lymphocytes, plasma cells and foreign body giant cells which may contain the acid-fast spores. The whole forms a *lycopodium granuloma* (Fig. 308). Similar lesions are produced by talc powder, which consists of crystals of magnesium silicate, and also by sulphur powder.

**TUBERCULOUS PERITONITIS.**—The peritoneum is infected with tuberculosis either from an abdominal organ or from outside the abdomen. There are three chief intra-abdominal sources: (1) tuberculosis of the bowel, (2) tuberculous mesenteric glands, and (3) tuberculosis of the Fallopian tube. In the first and third of these the infection may be limited to a few tubercles on the outside of the intestinal ulcer or the infected tube. We are concerned here with general infection of the membrane. Repeated infection may occur through the ostium of the tube, so that no treatment is of avail until the tube is removed, but usually the ostium is sealed up by

adhesion of the fimbriæ. The extra-abdominal sources are the lungs and pleura (probably lymph spread through the diaphragm), and a distant focus in bones, joints, or bronchial lymph nodes (blood spread). The disease is commoner in children and young adults, and occurs in two main forms, the moist and the dry.

In the *moist form* the chief feature is the great distention of the abdomen, with its tight shiny dome overtopping the wasted body of the patient. The distention is caused by a great accumulation of thin, watery, pale yellow fluid which shows the characteristics of an exudate, *i.e.*, a specific gravity above 1018 and an albumin content about 4 per cent. It contains many lymphocytes and may be blood-stained. Blood in the abdominal fluid suggests tuberculosis or malignancy of the peritoneum. When

the fluid is removed the surface of the peritoneum is seen to be studded with miliary tubercles. Sometimes the tubercles excite the formation of a plastic exudate which covers up and hides the tubercles. There may be larger caseous masses and the mesenteric lymph nodes are usually large and caseous. The omentum may be thick and contracted, but this is more characteristic of the dry form. Occasionally the fluid may be encysted by adhesions, so as to simulate an abdominal cyst. Opening of the abdomen and drainage of the fluid is often followed by remarkable improvement which



FIG. 308.—*Lycopodium* granuloma showing spores, giant cells and fibrosis.  $\times 75$ .

is difficult to explain, but unless the primary focus (Fallopian tube, etc.) is removed a permanent cure cannot be expected. The injection of oxygen into the peritoneal cavity also gives good results.

In the *dry form* there is little or no fluid, but a dense plastic exudate is produced which glues the intestines together and is followed by the formation of very firm adhesions. When the abdomen is opened the coils of intestine are matted together and cannot be separated, so that a detailed examination of the bowel for tuberculous ulcers may be a matter of great difficulty. The surface may be studded with tubercles, but often these are completely covered by the inflammatory exudate. The omentum is thickened and contracted so that it forms a flat mass like a pancake, or a rounded one like a sausage which can be felt through the abdominal wall. When the coils of bowel are partially separated collections of fluid may be found between them. A fecal fistula may be formed owing to a loop of diseased bowel becoming adherent to the abdominal wall, followed by caseation of the wall and ulceration of the skin surface. The fistula may open at the umbilicus.

### TUMORS OF THE PERITONEUM

**SECONDARY CARCINOMA.**—The peritoneum may be infected from carcinoma of any intra-abdominal organ. There may be one or two masses

in the mesentery and omentum, or a condition of diffuse carcinomatosis. The primary tumor is usually in the stomach, large bowel, or ovary (malignant papillary cystadenoma). The infection is caused by the tumor perforating the serous coat and scattering cells over the serous surface. The connection between the tumor on the inside and the tumor on the outside may be very evident to the naked eye, or the process of serous invasion may be seen only with the microscope. Tumor cells from a cancer of the stomach may drop down through the peritoneal cavity, forming little implantations on the serous surface to mark their track, and becoming seeded on the pelvic organs where they may form secondary growths. The ovaries form particularly favorable soil, and may present large tumors before a cancer of the stomach is suspected. Lymphatic spread may result in widespread dissemination. In such cases the wall of the bowel may be covered with a fine network of white lines representing lymph vessels distended by tumor cells. The irritation of the peritoneum causes ascites to develop, and carcinoma cells may be found in the fluid. Unless the cells are in clumps it is very unsafe to diagnose them as indicating malignancy. The fluid is often hemorrhagic.

If the primary tumor is a colloid type of carcinoma, the secondary growths form large soft jelly-like masses. The curious condition of *pseudomyxoma peritonei* may be caused by rupture of a pseudomucinous cyst of the ovary and more rarely of a mucocele of the appendix. This condition, which is not really malignant, is considered in connection with ovarian cysts.

*Primary tumors* are so extremely rare that they need only be mentioned. It is said that a primary endothelioma of the peritoneum may occur in the form of a diffusely infiltrating tumor.

**RETROPERITONEAL TUMORS.**—These are rare tumors growing from the retroperitoneal connective tissue of the posterior abdominal wall. The chief of them is the lipoma and sarcoma.

*Retroperitoneal lipoma* is really a mixed tumor, although consisting largely of fat. Some parts are myxomatous and some sarcomatous. It commences at one side of the vertebral column, usually at the level of the kidney, grows very slowly, and may reach an enormous size, filling the greater part of the abdominal cavity. It may creep through the intervertebral foramina and compress the cord. The tumor is more nearly related to the teratomata than to an innocent lipoma, and may occur in early childhood, although usually in middle age.

*Retroperitoneal sarcoma* is a fibrosarcoma which grows from the fascia of the posterior abdominal wall. It shows the usual gross and microscopic characters of a fibrosarcoma.

### MESENTERIC CYSTS

Cysts of the mesentery and omentum are rare. *Lymphatic cysts* of the mesentery are probably lymphangiomata of congenital origin. They occur in childhood and early adult life. They are usually single and about the size of a hen's egg, but may attain a great size. The lining is a flat endothelium, and the contents are watery or milky. *Gas cysts* of the mesentery are very rare in humans, though common in the pig. They are quite small and are usually grouped in one segment of the bowel. Their nature is uncertain; the gas may be formed by bacteria, or may be produced by cells. *Hydatid cysts* are fairly common in the mesentery, where they form multiple masses which may reach a large size.

### ASCITES

Ascites is an accumulation of serous fluid in the peritoneal cavity, so that the abdomen becomes converted into a bag of fluid (*askos*, a bag). The fluid may be dropsical in origin, *i.e.*, a transudate, or inflammatory, *i.e.*, an exudate. *Dropsical ascites* may be part of a general dropsy due to cardiac or renal disease, or it may be due to obstruction of the portal vein. Portal obstruction is usually caused by portal cirrhosis of the liver, but may be due to pressure on the vein by a tumor, enlarged glands, etc. The *exudative form* of ascites is caused by irritation of the peritoneum by tuberculosis or carcinomatosis, and the fluid may contain blood. Ascites in a woman with normal heart and kidneys should suggest carcinoma of the ovaries. The inflammatory fluid has a higher specific gravity (above 1018) and protein content (above 3 per cent) than the dropsical fluid.

PICK'S DISEASE.—This condition has already been discussed under the heading of chronic constrictive pericarditis, but it is mentioned here because the most striking features may be great thickening of the peritoneum and recurring ascites. In one case which I examined when the abdomen was opened it looked as if the viscera had been removed, so marked were the pressure effects of the ascites and so great was the peritoneal thickening. There is often a polyserositis, affecting peritoneum, pericardium, and pleura.

### THE ABDOMINAL WALL

The abdominal wall suffers from the same pathological conditions as the rest of the surface of the body, but a few lesions deserve separate mention.

**Tumors.**—A *lipoma* of the subcutaneous tissue is not uncommon. It must be differentiated from small extrusions of extraperitoneal fat in the middle line of the epigastric region.

The *fibroma* or *desmoid tumor* grows from the sheath of the rectus and tends to infiltrate the muscle. It is densely hard, and interlacing bands of fibrous tissue are seen on the cut surface (*desmos*, a band). About 80 per cent of the cases occur in women who have borne children. In the remaining cases there is usually a history of injury to the abdominal wall. The enclosed muscle fibers may become converted into multinucleated plasmodial masses like giant cells. Some of these tumors show a tendency toward malignancy, recurring repeatedly after removal.

ACTINOMYCOSIS.—When the cecum or appendix is the seat of actinomycosis, the infection may spread to the overlying abdominal wall, appearing as a hard swelling in the right groin. This softens and discharges pus containing the characteristic sulphur granules.

OSSIFICATION OF ABDOMINAL WALL.—In rare cases bone may be formed in the scar of a laparotomy wound. This usually occurs above the umbilicus, and appears to be an example of metaplasia of one form of connective tissue into another form. It has also occurred in the hypogastrium following operations on the bladder (prostatectomy, etc.). This is more readily understood, for Huggins has shown that bladder mucosa transplanted into the abdominal wall gives rise to bone formation, although with no other mucous membrane was a similar result obtained.



**LESIONS OF UMBILICUS.**—The umbilicus, though a small structure, suffers from many diseases, as may be seen in Cullen's monograph of 650 pages. The most important lesions are congenital anomalies, fistulæ and tumors.

**Patent Vitelline Duct.**—The vitelline or omphalo-mesenteric duct, the original communication between the intestine and the yolk sac which normally becomes closed at the end of the second month of intra-uterine life, passes from the ileum a short distance above the ileocecal valve to the umbilicus. When the intestinal end remains open it is called *Meckel's diverticulum*; this is a common condition. Rarely the entire tract remains open, so that the intestine communicates with the surface; this is known as a patent Meckel's diverticulum. The distal end only may remain open while the intra-abdominal part is obliterated; the mucous membrane is prolapsed on the surface to form a raspberry-like tumor. If both ends are closed but the intervening portion remains open, a cyst is formed.

**Patent Urachus.**—The urachus is the communication between the urinary bladder and the allantois *via* the umbilicus. If it does not become obliterated, there is a fistulous opening at the umbilicus through which urine is discharged. A urachal cyst is formed if both ends of the duct are closed but the intervening part remains patent.

**Fistulæ.**—Examples of fistulæ of *congenital* origin have already been described. An abdominal *abscess* may point and rupture at the umbilicus. A *fecal fistula* is most often due to tuberculous peritonitis, a loop of diseased bowel becoming adherent to the umbilicus; caseation and breaking down then give rise to a fistula between the bowel and the skin.

**Tumors.**—Tumors of the umbilicus are usually *secondary carcinomas*. The primary growth is likely to be in the stomach, large bowel, gall-bladder or ovary, and is usually an adenocarcinoma. It feels like a hard button. The tumor cells may reach the umbilicus *via* the round ligament. Secondary cancer of the umbilicus is a late manifestation, and indicates that the case is inoperable.

**Primary carcinoma** is very rare, although I happen to have seen 3 cases. It is usually an epidermoid carcinoma, but may be an adenocarcinoma. It is probable that most of the latter cases reported in the literature are really secondary. *Endometrioma* is an interesting tumor, in the form of a small red nodule from which blood may be discharged at the menstrual period. It consists of endometrial tissue (see discussion on Endometriosis). It is also known as an adenomyoma, because it may contain both glandular and muscular tissue.

## ADDITIONAL READING

- Acute Peritonitis.** HANDEY: Brit. J. Surg., 1925, 12, 417. STEINBERG: Arch. Surg., 1931, 23, 145.  
**Bone Formation of Abdominal Wall.** HUGGINS: Arch. Surg., 1931, 22, 377.  
**General Reference.** HERTZLER: The Peritoneum, Philadelphia, 1919.  
**Lycopodium Peritonitis.** AUTOPOL: Arch. Path., 1933, 16, 326. ERB: Surg., Gynec. and Obst., 1935, 60, 40.  
**Pneumococcal Peritonitis.** MCCARTNEY AND FRASER: Brit. J. Surg., 1922, 9, 479.  
**Subphrenic Abscess.** DOHERTY AND ROWLANDS: Brit. Med. J., 1931, 1, 168.  
**Talcum Granuloma.** FIENBERG: Arch. Path., 1937, 24, 36.

## Chapter

## 24

# THE URINARY SYSTEM

## THE KIDNEYS

**DESCRIPTIVE OUTLINE.**—It is of particular importance in describing so complex an organ as the kidney that a definite order should be followed, otherwise essential points may be omitted. These points are as follows: size, weight, consistence, capsule, cortex, medulla, arteries, pelvis. The *size* is fairly constant in health; if only one kidney is present it will be twice the normal size and weight. The length is about 11 cm., the breadth 6 cm., and the thickness 3 cm. The kidney substance may be divided into lobules by deep grooves, a condition known as fetal lobulation and of no pathological significance. The average *weight* is 150 grams. The *consistence* is such that when held horizontally by the middle, each end tends to dip slightly. If softer than normal, the kidney may form the arc of a circle when held by the middle. If the consistence is increased (amyloid), there is no dipping even when it is held at one end. The *capsule* is thin, translucent, and can be readily stripped off, leaving a smooth surface. If it has become adherent as the result of disease, pieces of cortex may come away when attempts are made at removal (decortication). The *cortex* between the base of the pyramid and the capsule is 5 mm. wide; the deep cortex lies between the pyramids. The color of the cortex is reddish-brown; it may be pale due to ischemia, yellow due to lipoid deposits or fatty degeneration, or dusky red due to congestion. The cortex is traversed by fine alternate red and gray lines, best seen by means of a hand lens. The red lines correspond to the interlobular vessels, the gray lines or medullary rays to the collecting tubules and parts of the loop of Henle passing down into the medulla. These cortical markings become distorted or completely lost in chronic Bright's disease. The boundary zone of the *medulla* shows a continuation of the cortical markings. The papillæ projecting into the pelvis are inspected for early lesions of tuberculosis. The condition of the *arteries*, best seen at the base of the pyramids, is noted; their walls are thickened in hypertension. The *renal pelvis*, with a capacity of 7 to 10 cc., is lined by a smooth, glistening, grayish-white mucous membrane in which no vessels should be visible.

The *microscopic description* includes glomeruli, tubules, interstitial tissue, and arteries. Each glomerulus consists of a glomerular tuft, a capsular space, and Bowman's capsule lined by flattened epithelium. The glomerular tuft is made up of capillary loops, each of which presents a basement membrane lined by endothelium and covered by epithelium, the latter being continuous with the epithelium lining Bowman's capsule and with the tubular epithelium. With appropriate staining it becomes apparent that there are two basement membranes, a thick epithelial membrane and a delicate endothelial membrane. These are separated by an interstitial space which is only apparent in early childhood or under pathological conditions (edema, etc.). It contains a few connective tissue cells. The juxtaglomerular apparatus is a collection of cells at the vascular pole of the glomerulus in relation to the afferent arteriole, possibly concerned with the regulation of blood flow through the glomerulus.

For beautiful illustrations of the microscopic appearances in renal disease the reader is referred to the descriptive atlases of Allen and of McManus.

### BRIGHT'S DISEASE

In 1827 Richard Bright described a series of cases in which edema was associated with the presence of albumin in the urine, and which he correctly attributed to disease of the renal parenchyma, though guided by naked-eye examination alone. With the passage of time the conception of what was called Bright's disease became greatly widened, at least on the pathological side, so that now a number of different nonsuppurative inflammatory and degenerative conditions are included which bear a clinical resemblance to one another but which have a different pathological basis. It seems useful to retain the term Bright's disease, if only for sentimental reasons. The principal members of the groups are glomerulonephritis, nephrosis (glomerular and tubular), glomerulitis (toxic and thrombotic), arteriolar glomerulosclerosis, and pyelonephritis.

In Bright's disease the structures *primarily* affected may be the glomeruli (glomerulonephritis), tubules (nephrosis), arteries (arteriolar nephrosclerosis), or interstitial tissue (pyelonephritis). The glomeruli may be blocked (glomerulonephritis), or leaking owing to damage to the basement membrane (lipoid nephrosis).

### GLOMERULONEPHRITIS

Diffuse glomerulonephritis is an inflammatory condition affecting the glomeruli primarily, but with secondary damage to the other parts of the nephron as well as the interstitial tissue later. It is the condition which should be understood when the word nephritis is used without qualification. The glomerulonephritis is diffuse in distinction to other less important forms of focal glomerulonephritis. The pathology and symptomatology of glomerulonephritis vary to such an extreme degree that three different forms have been described under the names acute nephritis, subacute or subchronic nephritis, and chronic nephritis. It has long been believed that these forms correspond to three stages of one disease (Volhard and Fahr). It is true that in most cases it is difficult or impossible to detect a transition from one stage to the other clinically, but it has been assumed that the second and third stages are preceded by subclinical acute attacks. Moreover, in the occasional case there is a well defined progression through the acute and subacute to the chronic stage. This concept has been forcibly challenged by Ellis and his associates at the London Hospital, a challenge to which reference will be made when the etiology and lesions have been discussed.

The *acute stage* is characterized clinically by urinary evidence of acute inflammation, signs of acute renal insufficiency, edema, and a varying degree of hypertension. In the *intermediate stage*, also called *subacute* and *subchronic*, there is edema and albuminuria. The chief features of the *chronic stage* are hypertension and renal failure. Recovery is usual after

the first stage, but repeated subinfections may cause the kidney to pass through all three stages if the patient survives long enough.

**Etiology.**—Acute diffuse glomerulonephritis is an acute non-suppurative proliferative inflammation in which no bacteria can be demonstrated. It frequently follows an acute streptococcal infection, usually in the throat. In infectious disease hospitals it often follows scarlet fever in children after an interval of two or more weeks, and in throat infections there is often an interval. This latent period, together with the absence of bacteria and the peculiar proliferative type of lesion, strongly suggests that sensitization of the tissue is an essential feature and that the inflammation is allergic in character due to an antigen-antibody reaction in the glomerulus, perhaps the most vulnerable part of the whole vascular system.

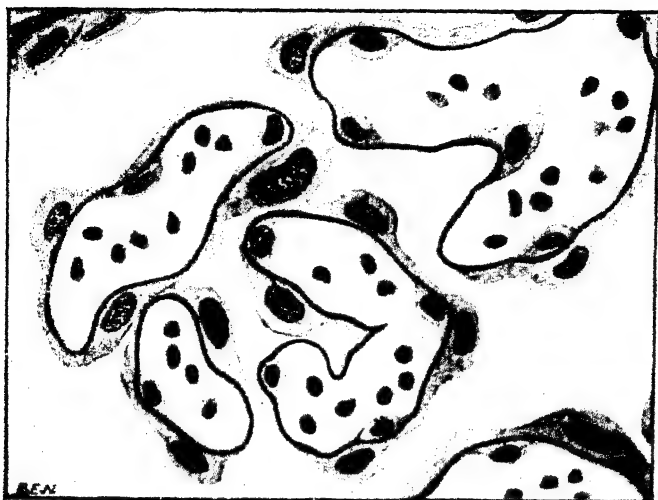
Hypersensitivity is also the factor common to all types of experimental glomerulonephritis. This state may be induced by a variety of antigens, such as bacteria and their products and foreign proteins. The two methods most successful in reproducing the human type of lesions in animals have been the use of bovine serum gamma globulin (More and Waugh), and Masugi's so-called nephrotoxic serum, which is a specific antibody prepared by immunizing an animal of one species with a suspension of kidney tissue from another species. When the glomeruli are separated from the other renal components, as can readily be done, and are used as antigen, a potent nephrotoxic serum is produced, whereas all other cortical components are without effect (Green and Krakower). Cavelti and Cavelti have approximated the actual conditions of the human disease by showing that beta hemolytic streptococci are able in some way to render renal material antigenic in the same species of experimental animal. The antigenic material so formed when carried to the kidneys by the blood would excite the formation of autoantibodies which unite with the kidney with the production of progressive glomerulonephritis.

Two contributing factors which may play a part are cold and diet. There seems to be a close relation between the vessels of the skin and those of the kidney. When the skin of an animal is chilled there is a transient albuminuria, due probably to vasoconstriction of the glomerular capillaries followed by dilatation. In experimental glomerulonephritis diet has a marked effect both on the course of the nephritis and on the lesions. On a low-protein-high-carbohydrate diet the animals are likely to recover, whereas on a high-protein-low carbohydrate diet they are likely to die of progressive nephritis. The seat of the greatest damage in the high protein group is the proximal convoluted tubule.

In *chronic* glomerulonephritis which has been preceded by an acute attack there may be clinical evidence of subsequent recurring infections. In the great majority of cases, however, there is no hint as to an etiologic factor, and any suggestions are mere guesswork.

**SYMPTOMS.**—The symptomatology of glomerulonephritis is so diverse that little is to be gained by giving a list of symptoms at this stage. Some of the principal ones will be discussed when the relation of symptoms to lesions is considered. It may be useful, however, to indicate some of the possible courses which the disease may follow. The clinical picture may vary to such a degree that it is difficult for the observer to convince himself that the different patients are merely suffering from

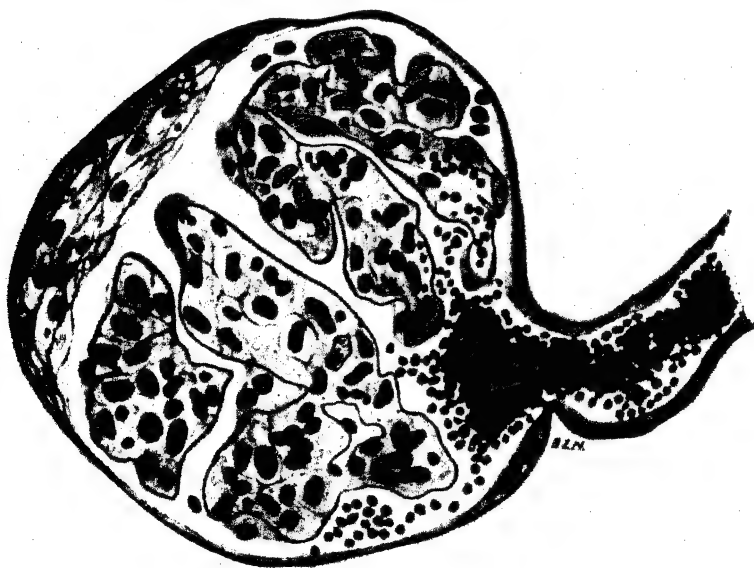
# PLATE XVI



A

**Normal Glomerulus.**

The capillary loops show numerous epithelial cells, a few endothelial cells, and the basement membrane. (Azocarmine.)



B

**Glomerulonephritis.**

The lumen of the capillaries is almost entirely filled with proliferated cells. There is an epithelial crescent at one side. The capsular space and the tube contain red blood cells. (Azocarmine.)

variations of one central theme. The chief of these variations are as follows. (1) The patient may die of uremia early in the *acute stage*, with marked albuminuria, hematuria, edema, slight hypertension, and retention of non-protein nitrogen in the blood. A not uncommon cause of death at this stage is left ventricular failure, the explanation of which is uncertain. The majority of the acute cases recover completely in the course of a few months. (2) He may survive the acute phase of the attack, but the features of the first stage may continue or become more pronounced until uremia develops and the patient dies in the course of a few months. (3) In the so-called *second* or *subacute stage* there is usually no history of an acute attack, so that there is no real proof that the stage is secondary. The dominant features are edema and massive albuminuria, which in the absence of hypertension constitute the nephrotic syndrome. Sooner or later hypertension and impairment of renal function make their appearance, often with a coincident disappearance of the edema. The duration of this stage is variable. Usually within a period of two years the patient either dies of an intercurrent infection, to which he is very susceptible, or passes into the third stage. In some cases, however, the stage of edema lasts for many years. (4) The majority of patients in the *chronic stage* present no history of an acute attack. The blood pressure rises gradually as renal insufficiency increases; this is in striking contrast to essential hypertension in which high levels are attained early in the disease. A history of cerebral hemorrhage or coronary heart disease is rare, again in marked contrast to essential hypertension. The blood non-protein nitrogen shows a slow progressive rise until the terminal stage, when the rise becomes sudden. The average time between the acute attack and death in the chronic stage is about ten years, but it may be much shorter or considerably longer.

**LESIONS.**—*Acute Glomerulonephritis.*—Both kidneys are always involved in diffuse glomerulonephritis. The gross appearance is not especially characteristic. The kidneys are usually swollen, and the capsule is tense. The pale cut surface suggests cloudy swelling.

*Microscopically* the essential lesions are in the glomeruli. Practically all the glomeruli are involved, so that it is a true diffuse nephritis; such a picture could only be produced by the action of a diffusible toxin. The glomeruli are swollen so as completely to fill the capsular space. They are more cellular than normal, for reasons which will soon become apparent.

The best idea of the process is to be obtained by a consideration of one of the capillary loops of which the glomerular tuft is composed (Fig. 309). The epithelium has a heavy and the endothelium a fine basement membrane which are best shown by the McManus stain (PAS, periodic-acid Schiff reaction). The two membranes are separated by the interstitial space and tissue, continuous with a corresponding space and tissue in the stalk of the glomerular lobules. In Plate XVI, A only a single membrane and no interstitial space is shown. Rinehart speaks of the basement membrane as having two components, epithelial and endothelial. With his colloidal iron method the epithelium stains blue, the endothelium yellow, and the basement membrane reddish violet. The interstitial tissue, which is most abundant and easily observed in the child, or when the two membranes are separated by edema and exudate, normally contains a number of connective tissue cells which increase with age and injury. In acute inflammation the space is invaded by inflammatory cells and occupied with proliferating interstitial cells. The characteristic lesion of acute glomerulonephritis is the greatly increased cellularity of the tuft (Plate XVI, B), which seems to be

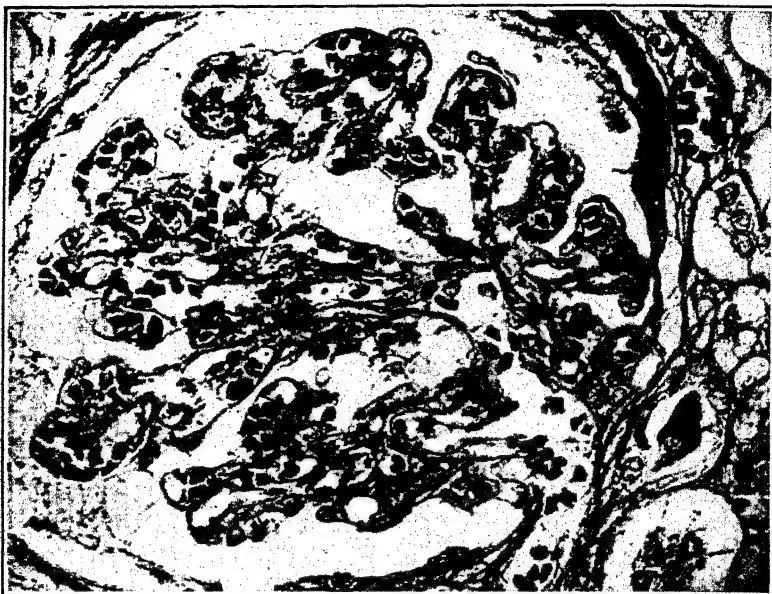


FIG. 309.—Glomerulus, showing individual units, the capillary loops of which the tuft is composed, widely separated.  $\times 400$ .



FIG. 310.—Glomerulonephritis, showing cellular proliferation and avascularity of the tuft. The case is in the intermediate stage; epithelial crescent to left.  $\times 450$ .

due largely to the cells in the interstitial space and not merely to proliferation of the vascular endothelium which is the usual view. These changes are beautifully illustrated in Jones' paper. An earlier but less important change is swelling and multiplication of the epithelium of the tuft, so that the cells fill the spaces between the loops. Later they undergo degeneration and are cast off into the capsular space. Polymorphonuclear leucocytes collect in large numbers in the glomerular capillaries, and there is a varying amount of exudate (serum, fibrin, leucocytes and red cells) in the capsular space, which passes into the urine. The proliferating interstitial cells give rise to the formation of fibrils and later of connective tissue as healing proceeds. This causes an all-important obliteration of the capillary bed of the glomerulus, a process which may be aided by proliferation of the vascular endothelium.

As a result of the proliferative changes the loop becomes occluded and bloodless (Fig. 310). The other loops of the tuft share in the change, with the result that little or no blood flows through the glomerulus. The blood supply to the tubules passes through the glomeruli, so that the ischemia will lead to secondary tubular degeneration and in turn to increase of the interstitial fibrous tissue. These changes, however, are not seen in the first stage of nephritis.

The *further course* may be toward *healing* or *chronicity*. In the scarlatinal cases there is usually complete recovery, and if the patient dies some years later the glomeruli may show no trace of former lesions; in other cases a greater or less number of glomeruli are found to be obliterated. In other cases, especially those due to streptococcal infections of the throat, the kidney

is exposed to repeated reinfection, so that the process advances to the second and finally the third stage of nephritis. As regards the microscopic changes the *first stage* is the stage of *proliferation*, the *second* is the stage of *degeneration*, and the *third* is the stage of *atrophy* and *scarring*.

*Subacute Glomerulonephritis.*—The gross appearance is well described by the old term "large white kidney" (Fig. 311). The kidney is slightly or considerably enlarged, the capsule strips easily, and the exposed surface is smooth and pale. The cut surface shows marked swelling and pallor of the cortex, in comparison with which the pyramids appear unnaturally dark. The pallor is due chiefly to a great accumulation of lipid in the cells of the convoluted tubules, but in part to emptying of the capillaries from swelling of the parenchyma. There may be bright yellow streaks and



FIG. 311.—Kidney in the intermediate stage of glomerulonephritis; the "large white kidney".



patches in the cortex due to large deposits of lipid. The consistence is soft.

*Microscopic examination* shows a picture of degeneration combined with a varying degree of the proliferation of the first stage and the atrophy and scarring of the third stage. It is naturally impossible to draw too hard and fast a line between the different stages, and one part may show more proliferative lesions, while another part shows atrophy. The intermediate stage differs from the acute in the important respect that all three of the main constituents of the kidney are involved—glomeruli, tubules, and arteries—as well as the interstitial tissue.

The *glomeruli* show an advancement of the changes of the first stage. The degree of vascular occlusion probably determines the clinical course.

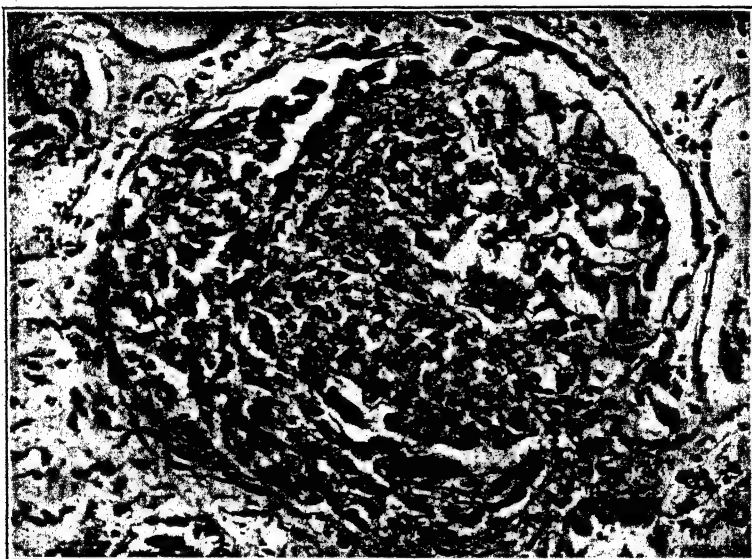


FIG. 312.—The epithelial crescent of glomerulonephritis. The space between the tuft and Bowman's capsule is occupied by proliferated epithelial cells.

The more severe and widespread the occlusion, the more quickly will the kidney pass into the atrophic stage. Some of the glomeruli are converted into structureless hyaline masses through which no blood can pass and which can secrete no urine into the tubules. The hyalinization is due to a gradual increase of the hyaline fibers which begin to be formed in the acute stage.

*Capsular changes* are also present. Red blood cells, desquamated epithelium, albumin, and fibrin are present in the capsular space in varying amount. The chief change is a proliferation of the capsular epithelium. Large masses of cells are formed which occupy the capsular space. The whole circumference of the glomerulus is seldom involved, so that the cells form a semilunar mass in the capsular space which is known as the *epithelial crescent*, and provides the most easily recognized evidence of glomerulo-

nephritis (Fig. 312). The crescent is a reaction to the presence of red cells in the capsular space. It may, therefore, be seen in such hemorrhagic lesions as the glomerulitis of malignant hypertension and subacute bacterial endocarditis. In course of time the crescents become fibrosed and fuse with the hyaline tuft.

The *tubules* show marked degenerative changes, which are most pronounced in the convoluted tubules. The epithelium of the convoluted tubules shows cloudy swelling, fatty degeneration or necrosis. The fat content may be very high. In addition to neutral fat the cells may contain large amounts of lipid material, chiefly cholesterol ester, which can be seen as bright anisotropic globules in frozen sections under crossed Nicol's prisms. As the tubular degeneration progresses, many of the epithelial cells are cast off and the tubules become atrophic.

*Chronic Glomerulonephritis.*

—This is the *stage of scarring*. In an advanced case the kidney is small and shrivelled, its surface is covered with fine granules, and the capsule is so adherent that, when it is stripped off, portions of the cortex come away with it (decortication) (Fig. 313). The meaning of the granularity is shown by the microscopic examination. Sometimes the surface may be smooth even though the microscopic changes are marked. The cut surface shows extreme irregularity and atrophy of the cortex, which in places may be only 1 or 2 mm. in width. The irregularity corresponds with the granularity of the surface.

The normal vertical markings of the cortex produced by the vasa recta are lost.

*Microscopic examination* shows almost complete loss of the renal architecture. The parenchyma, which normally consists practically entirely of tubules with a few scattered glomeruli, has been replaced by the cheap substitute of fibrous tissue. It is this disappearance of tubules which strikes the observer most on first examining the section.

The *glomeruli* show hyalinization in its most extreme form. Owing to the disappearance of the tubules and the shrinkage of the cortex there may be large numbers of hyaline glomeruli in a low-power field (Fig. 314). Other glomeruli are atrophic and shrunken, but their capillaries still allow



FIG. 313.—Chronic glomerulonephritis (granular contracted kidney).

the passage of some blood. Still other glomeruli are greatly hypertrophied. It is these which carry on the work of the kidney and keep the patient alive. The hyaline glomeruli fade away and blend with the surrounding tissue until they can no longer be distinguished.

The *convoluted tubules* show an extreme degree of atrophy, and only their outline may be detected under the high power. Some of the tubules appear normal or more often are dilated and lined by a high epithelium with papillary buds projecting into the lumen, although when the dilatation is



FIG. 314.—Complete hyalinization of glomeruli with disappearance of tubules in center of field and round-cell infiltration.  $\times 60$ .

marked the cells become low or even flattened. These tubules, which are connected with hypertrophied glomeruli, may be regarded as showing evidence of compensatory or work hypertrophy. They are collected in little groups which stand out in striking contrast to the rest of the shrunk parenchyma, and it is these islands of tubules which, projecting above the surrounding surface, give rise to some of the granularity. Microdissection has shown that a hypertrophied tubule may be attached to a completely atrophied glomerulus, suggesting the condition found in the aglomerular

kidney of certain fish where the tubule plays the part of the glomerulus (Oliver).

The *interstitial tissue* shows a very great increase, which is mostly apparent due to the concentration of tissue, but to some extent is real. Groups of small round cells may form a striking picture in the fibrosed cortex especially in the neighborhood of the hyalinized glomeruli.

The *arteries* supplying the fibrosed atrophic areas show the changes of disuse atrophy, the chief feature of which is marked fibrous thickening of the intima causing narrowing of the lumen. This is a form of endarteritis obliterans similar to the change which occurs when a vessel is ligated. If hypertension becomes marked, hypertensive vascular lesions may develop (see page 569), some of which unfortunately may resemble those of disuse atrophy. The chief of these hypertensive vascular lesions is arteriosclerosis with marked narrowing of the lumen. This may have two effects: (1) by causing renal ischemia it may accentuate the hypertension, which in turn leads to further arteriosclerotic ischemia, so that a vicious circle is set up; (2) by depriving the remaining nephrons of their blood supply it may add the *coup de grâce* to the already faltering kidney and bring about its final downfall.

**The Ellis Concept.**—As already indicated, Ellis and his associates at the London Hospital have called in question the concept of Volhard and Fahr that glomerulonephritis is a single entity with varying manifestations and three stages. This is the result of a study of the natural history of the disease in some 600 cases over a period of twenty years with post-mortem examination of 200 of the cases. The conclusion reached is that there are two different kinds of glomerulonephritis, with different etiology, lesions, course and prognosis. These they call Type 1 and Type 2 nephritis.

*Type 1* corresponds with first stage or acute glomerulonephritis. It is identical in etiology, age incidence and lesions. There is gross hematuria of abrupt onset a week or two after an acute infection. About 85 per cent of cases make a complete recovery. In 10 per cent the albuminuria persists, and in the course of years hypertension and renal failure with contracted kidneys develop as in the usual concept, but without a picture of nephrosis.

*Type 2* has a remarkable insidious onset with progressive edema and albuminuria but no history of an acute infection or gross hematuria. The etiology is unknown. The progress is slow but remorseless, and at least 95 per cent of cases die either from infection resulting from loss of gamma globulin or from renal failure associated with hypertension. The basic lesion is a slow thickening of the capillary basement membrane with progressive hyalinization of the glomerular tufts. This type corresponds with the second stage of Volhard and Fahr with eventual development of the third or sclerotic stage.

The future will show whether it is better to postulate two unrelated forms of glomerulonephritis or to stick to the concept of three possible stages of a single process. In this connection reference may be made to the experimental work of Teilum and his associates who in hyperimmunized rabbits produced the proliferative Type 1 lesion of Ellis by intravenous injection of killed bacterial culture in some animals but the hyalinized type

2 lesion in other animals. Moreover, it was possible to change type 1 into type 2 lesions by the administration of cortisone. It may be that the adrenal cortex conditions in some way the response of the glomerular tufts in antigen-antibody reactions.

THE RELATION OF SYMPTOMS TO LESIONS.—*Albuminuria* is of glomerular origin, being due to damage to the renal filter. This filter is a very delicate affair, which may be interfered with by processes which leave no anatomical trace. Thus mere clamping of the renal artery for thirty seconds will cause albuminuria due to temporary anoxia. Albuminuria is present in the acute stage, but it is most massive in the so-called second stage. Here it is commonly associated with ascites, the combination constituting the nephrotic syndrome.



FIG. 315.—Albuminous fluid in the glomerular space in a case of nephrotic edema.  
× 150.

*Renal edema* may be divided into nephritic edema and nephrotic edema. *Nephritic edema* occurs in acute glomerulonephritis. It is evidently due to an increased permeability of the capillaries, because the fluid in the tissues contains over 1 per cent of protein, a condition which Eppinger has called "albuminuria into the tissues." The capillaries of the subcutaneous tissue are probably injured by the same toxins which act on the capillaries of the glomeruli. It is therefore an inflammatory form of edema. *Nephrotic edema* occurs in so-called chronic nephrosis, in the nephrotic or second stage of glomerulonephritis (wet nephritis), and in the amyloid kidney. The protein content of the dropsical fluid here is less than 0.1 per cent, *i.e.*, one-tenth that of nephritic edema. It is evident that the mechanism of production of the edema must be quite different. Here there is great loss of plasma protein through the heavy albuminuria (Fig. 315) with particular loss of the albumin as shown by the reversed albumin-globulin ratio. The colloid osmotic pressure of the plasma is therefore diminished, and fluid is free to escape into the tissues.

It is a curious but easily explained fact that chronic renal edema varies inversely with the degree of impairment of renal function. As long as a patient in the second stage of glomerulonephritis shows little or no sign of renal insufficiency, the edema is marked. When renal insufficiency develops, the edema disappears. The reason is that obliteration of the leaking glomeruli stops the loss of albumin as well as paralyzes renal function, the blood proteins rise with an accompanying increase of the colloid osmotic pressure, and the fluid is drawn from the tissues back into the blood.

*Hypertension*, moderate in degree, occurs in about one-third of the acute cases. It becomes much less and sometimes disappears entirely in the second stage. In the third stage it forms one of the dominating features, but seldom attains the extreme degree seen in essential hypertension, and usually remains under 200 mm. The relation of the kidney to hypertension is discussed on page 577.

*High non-protein nitrogen*, which may be taken to indicate a retention of non-protein, is due to insufficiency on the part of the renal glomeruli. It is moderate in the first stage, disappears in the second stage, and may become extreme in the third stage. Its presence does not necessarily indicate the presence of nephritis, for it may be due to extrarenal causes such as the production of more urea than can be excreted (leukemia, etc.). Even when renal in origin there may be no nephritis, for in the stasis or cardiac kidney associated with a failing circulation the non-protein nitrogen may be raised.

*Blood cholesterol* is increased in nephritis with edema. It may be very high in the nephrotic stage. In acute nephritis the increase is moderate, while in the third stage it is normal or below normal. The meaning of the increase is not known. It is possibly due to some extrarenal disturbance of lipid metabolism. Although associated with edema it does not appear to be related to it. The distinction between nephritic and cardiac edema is sometimes quite difficult. Here the blood cholesterol is of great value, for while high in nephritic edema it is normal in the edema of heart failure.

*Uremia* is a symptom-complex too varied in its manifestations to be considered here in detail. (1) The symptoms may be *cerebral*, with excitement, apathy, muscular twitchings, convulsions, and coma; (2) they may be *gastro-intestinal*, with vomiting and diarrhea; or (3) they may be *pulmonary*, with the dyspnea of acidosis. The condition is evidently a toxemia, but the nature of the toxin is unknown. Although always associated with the retention of urea in the blood, it is not caused by the urea. It is probable that different toxic products of metabolism may be at work in different cases. Uremia is the final manifestation of renal failure. Occasionally it is a cause of death in acute nephritis. It constitutes the usual termination of the chronic stage. Tiredness, both physical and mental, is a characteristic feature of chronic uremia. When tissues from a case of uremia are fixed in a solution of xanthidrol in glacial acetic acid, masses of crystals of xanthidrol urea are found in the cerebral cortex and other organs (xanthidrol reaction) (Fig. 316). The reaction is of value in determining whether or not a pericarditis or enteritis found at autopsy in a case of uremia should be considered uremic in nature. The brain in uremia



FIG. 316.—Xanthidrol urea crystals (dark field).  
× 300.

usually shows marked edema (wet brain). Uremic enteritis and pericarditis may be found at autopsy. The entire alimentary canal may be affected (dry and glazed tongue, foul mouth, uremic breath, stomatitis, enteritis). Necrotizing and ulcerative lesions are commonest in the lower part of the small intestine and the colon. Some workers believe that the lesions are due to urea retention; others say that they are unrelated to urea retention and caused by infection of mucosal hemorrhages (Jaffé and Laing). The lungs may present a characteristic picture in the x-ray film, the so-called butterfly shadow, with one wing of the butterfly in the region of the hilus on each side. Microscopically the alveoli in the affected area are filled with a heavy protein exudate into which fibroblasts penetrate with eventual fibrosis.

Anemia is a common accompaniment. The degree of the anemia is relative to the azotemia, and is rarely present unless the NPN is raised. In 80 per cent of cases there is hyperplasia of the marrow, mainly myeloid in type, but when the NPN is above 150 mgm. there is evidence of erythroid hypoplasia (Callen and Limarzi). The mechanism regulating the delivery of red cells to the blood stream seems to be at fault. The progress of the disease may be gauged by the fall in hemoglobin.

The *urine* varies with the type of nephritis. In the acute form the characteristic finding is red blood cells, in addition to albumin and casts, the latter consisting of protein from the glomerulus with contributions of epithelium and granular and fatty detritus from the tubules. Anisotropic, *i.e.*, doubly-refractive bodies, may be found in the urine in the second stage by means of Nicol's prisms. They consist of cholesterol ester, and are related to the deposits of cholesterol in the renal tubules. The polyuria is merely a compensatory mechanism whereby the failing kidney tries to excrete waste products. It has lost its concentrating power, and in order that the necessary amount of solids may be eliminated, a greatly increased quantity of fluid must be poured out. The loss of concentrating power is indicated by the low and fixed specific gravity, and is largely due to atrophy of the convoluted tubules whose essential function is absorption. This atrophy in turn is caused mainly by the loss of blood supply to the tubules.

Perhaps the best tests for renal function are as follows: for glomerular function, the urea clearance test (volume of blood cleared of urea in one minute's excretion of urine); for tubular function, the diodrast clearance test for tubular excretion, and the urine concentration test for tubular absorption. The urinometer, in the hands of one who knows how to use it, is in some ways a more potent weapon for estimating the functional capacity of the kidneys than the complex and expensive methods of blood chemistry. Finally the remark of an old writer may be borne in mind: "The good physician trusteth not the single witness of the water if better testimony be had. For reasons drawn from the urine alone are as brittle as the urinal."

### THE NEPHROSES

The term nephrosis has passed through many vicissitudes. It was first introduced by the pathologist to indicate that the principal lesion in a damaged kidney was tubular degeneration rather than glomerular inflammation. At a later date the clinician appropriated the word and applied it to a certain clinical picture characterized by marked edema and massive albuminuria, with in addition low plasma protein and high cholesterol, normal blood pressure and absence of signs of renal failure. If this condition is called the *nephrotic syndrome*, *i.e.*, a group of clinical features with no reference to tubular lesions, confusion can be avoided. Indeed, as will be seen presently, the basic lesion in such cases is glomerular rather than tubular.

Kimmelstiel has suggested a classification based on the concept that nephrosis is a metabolic disorder of the renal parenchyma associated with functional impairment. The condition, which is degenerative rather than inflammatory, may involve either the glomeruli (glomerular nephrosis) or the tubules (tubular nephrosis). Glomerular nephrosis is likely to be associated with the nephrotic syndrome of edema and massive albuminuria due to damage to the glomerular filter, as a result of which protein leaks through from the capillaries of the tuft into the capsular space; tubular nephrosis is associated with oliguria or anuria and terminal azotemia due to damage to the tubular epithelium, as a result of which water and electrolytes leak from the tubules into the interstitial tissue of the kidney and fail to reach the bladder, a condition of unselective tubular reabsorption. In glomerulonephritis oliguria is caused by too little excretion of water by the damaged glomeruli; in nephrosis it is caused by too much absorption of water by the damaged tubules.

**Glomerular Nephrosis.**—Noninflammatory lesions of the glomeruli in most instances are secondary manifestations of a process which is principally extrarenal, but they may represent a primary renal disorder. The principal varieties are lipid nephrosis, amyloid nephrosis, intercapillary glomerulosclerosis, wire-loop glomerulosclerosis, and the nephrosis of pregnancy.

**LIPID NEPHROSIS.**—The name of this condition is derived from the lipid deposits in the cells of the convoluted tubules and the presence of anisotropic lipids in the urine, but the basic lesion responsible for the functional disturbance is hyperpermeability of the glomerular capillaries for albumen, which pours from the plasma into the urine. The *glomerular capillary membrane* is thickened, due probably to a deposit of protein between its inner and outer layers, the condition called by Allen chronic membranous nephritis. This thickening may be overlooked unless a connective tissue stain is used, so that the glomeruli might be passed as normal, whilst attention is mistakenly focused on the tubules, the appearance of which is misleadingly dramatic but functionally unimportant. The capillaries of the tufts are not necessarily narrowed and may indeed be dilated. Such cases in the past have been erroneously regarded as "pure" or "genuine" tubular nephrosis without any glomerular component. They correspond to the type 2 nephritis of Ellis. The glomerular changes are strikingly uniform in their distribution. Indeed no glomerulus may be spared, and the changes in the individual tufts are equally diffuse. Sometimes there is what Allen terms a diffuse lobular glomerulonephritis, the tufts being sharply lobulated into a number of hyaline spheres of uniform size which are readily mistaken for the lesions of diabetic glomerulosclerosis or even for those of amyloid disease. A natural consequence of this widespread damage to the glomerular filter is severe protein depletion, which is not only the basis of the massive edema, but results in a loss of gamma globulin which exposes the patient to infections that are often fatal. If he should escape these dangers a slowly progressive glomerular obstruction will sooner or later be reflected in disappearance of the edema, the development of hypertension, and the onset of renal failure.

The *tubular lesions* attract the eye, but do not appear to interfere with renal function. The epithelium is loaded with lipids, both neutral fats and cholesterol esters, and it presents a striking appearance in frozen sections



stained with Scharlach R. The esters are best seen under crossed Nichol's prisms, the lipids appearing as bright doubly-refractive bodies. The tubular lesions are responsible for the *gross appearance*, which is that of the so-called "large white kidney" with pale swollen cortex presenting numerous yellow streaks and patches of lipids.

**AMYLOID NEPHROSIS.**—This condition is described later in this chapter (page 596). The glomerular lesions are the only ones of functional significance. Amyloid is deposited between the two layers of the glomerular capillary membrane with damage to the filter and the usual nephrotic sequelae. Later developments such as hypertension and contracted kidney are due to impairment of the renal circulation.



FIG. 317.—Capsular drop.

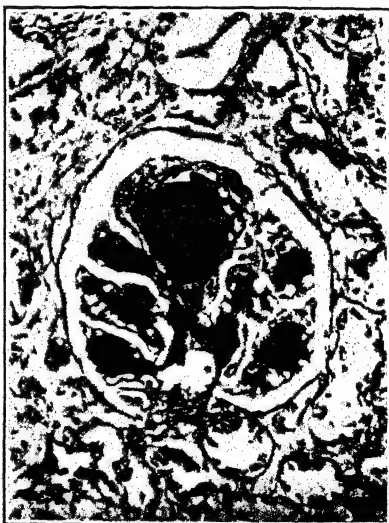


FIG. 318.—Intercapillary glomerulofibrosis.  $\times 120$ .

**Intercapillary Glomerulosclerosis.**—A peculiar and distinctive degenerative glomerular lesion has been described by Kimmelstiel and Wilson occurring in long-standing cases of diabetes often associated with hypertension, particularly in persons over forty years of age. Two forms have been described, the nodular and the diffuse. The *nodular* form is specific for diabetes, but is found in less than a third of the cases. It is the most reliable criterion for the histological diagnosis of diabetes in persons over the age of forty. It must be borne in mind that clinical evidence of diabetes may disappear with the onset of the intercapillary sclerosis and the development of renal failure. In the center of the tuft or in the center of one of the lobules there is a sharply localized hyaline mass suggestive of amyloid (Fig. 318). This is the result of a broadening of the intercapillary connective tissue. Some authorities (Bell, Allen) believe that the primary change is a splitting of the capillary basement membrane. Hartroft

suggests from evidence he has obtained both in the experimental animal and in the human diabetic that fat emboli plugging the glomerular tufts may cause exudation of plasma into and between the capillary walls with the formation of fibrin and eventually the true Kimmelstiel-Wilson lesion. It is conceivable, therefore, that a chronic form of intermittent fat embolism from fat deposits in the liver may be related to the glomerular lesions in diabetes. The *diffuse* form is non-specific for diabetes. It is a deposition of fibrillary and homogeneous hyaline material extending from the glomerular hilus to the periphery, and is merely an advanced degree of glomerular aging.

In addition to the classical Kimmelstiel-Wilson lesions, other glomerular changes, which may be called exudative lesions, are found in diabetics. Two of these are well illustrated in a paper by Barrie, Askanazy and Smith. The first they call the *fibrin cap*, a deposit of material giving the staining reactions for fibrin between the basement membrane and the tuft. The second they term the *capsular drop* (described in Kimmelstiel and Wilson's original paper), which is a drop-like formation of lipo-carbohydrate-protein beneath the parietal layer of epithelium (Fig. 317). It seems probable that fibrinogen and lipids escape from the diabetic blood and form these lesions. It should be emphasized that the renal lesions just described are not individually specific for diabetes, but a combination of two or more of these features are highly suggestive that diabetes was present.

Severe atheroma of the larger renal and intrarenal arteries is highly characteristic of diabetes. Indeed Hall believes that without these arterial lesions the glomerulosclerosis may be without clinical manifestations.

The clinical picture is likely to be nephrotic in type with massive albuminuria and marked edema; in mild cases there are no renal symptoms. A characteristic feature is the presence of lipoid or fatty cells and casts in the urine. They form a striking picture under the polarizing microscope, but are readily detected with ordinary light, and should at once suggest an investigation for diabetes. Although only recognized in 1936, diabetic glomerulosclerosis is now known to be more important numerically than chronic glomerulonephritis, and carries a constant threat to the diabetic of renal failure, hypertension, and blindness.

**WIRE-LOOP GLOMERULONEPHRITIS.**—This is a renal manifestation of disseminated lupus erythematosus. There is a patchy thickening of the glomerular capillary membrane with the occasional development of a nephrotic picture.

**NEPHROSIS OF PREGNANCY.**—*Eclampsia* is a complication of the latter part of pregnancy characterized by the nephrotic syndrome combined with hypertension and convulsions. In the absence of convulsions, which are probably secondary to the hypertension, the condition is called pre-eclampsia or the toxemia of pregnancy. The general aspects of the subject are discussed in Chapter 26. Renal lesions are present in every case. These represent a true glomerulonephrosis (glomerulosclerosis). Even in hematoxylin and eosin sections the glomeruli are seen to present a peculiarly solid appearance, with great narrowing or actual occlusion of the tuft. There may be some swelling of capillary endothelium, but connective tissue stains show that the essential lesion is a thickening of the capillary base-

ment membrane, or rather a widening of the interstitial space, at first by edema, so extreme in degree that a diagnosis of toxemia of pregnancy can be made from the renal picture. It will be realized that this lesion is similar in kind to that seen in lipoid nephrosis with the addition of narrowing or occlusion of the capillaries. The clinical picture is also that of the nephrotic syndrome with the all-important addition of arterial hypertension. The hypertension of toxemia usually disappears after delivery and removal of the placenta. This suggests that some hormonal pressor substance acting on the arteries is produced by the placenta. The permanent hypertension which sometimes develops may be due to glomerular ischemia. In very rare cases there is the condition known as symmetrical necrosis of the renal cortex (see page 594), in which complete cortical necrosis of both kidneys is associated with thrombosis of the small renal vessels with resulting uremia.

**Tubular Nephrosis**—The most important function of the kidneys is to maintain a normal and constant internal environment. In performing this function selective absorption by the tubules is as essential as excretion by the glomeruli. Damage to the tubules such as occurs in tubular nephrosis must interfere with this function, but the most striking result is oliguria or anuria. These causes of anuria may be divided as regards causation into two groups: (1) a large and important group in which the pathogenesis is uncertain, but which is probably anoxic or ischemic in nature; (2) a smaller and simpler group due to exogenous poisons such as mercuric chloride. These two groups may be termed anoxic nephrosis and toxic nephrosis.

*Anoxic Nephrosis*.—Oliguria and anuria associated with tubular degeneration may develop in a bewildering variety of extrarenal conditions. Examples of such conditions are shock, burns, trauma, severe hemorrhage, the crush syndrome, intestinal obstruction, dehydration, incompatible blood transfusion and blackwater fever. This group may be subdivided into (a) those cases which may be confidently attributed to renal ischemia, what Van Slyke has called the "shock kidney," and (b) cases of uncertain and mixed etiology where both ischemia and toxic factors may play a part, e.g. the crush syndrome, incompatible blood transfusion, etc. The same pathological changes are present in both, so that no attempt will be made to differentiate them. The onset of oliguria is often the first symptom, and is always a sign of ill omen. In the fatal cases death is due to uremia.

The kidneys are enlarged, the cortex pale from ischemia and swollen and the medulla dark and engorged. The main brunt of the attack falls on the boundary zone between the cortex and medulla, and the earliest lesions are seen in the loop of Henle and then in the second convoluted tubule which is a cortical extension of the ascending limb of the loop. For this reason Lucké, in his analysis of the very numerous cases of traumatic hemoglobinuric nephrosis seen in the Second World War, used the term lower nephron nephrosis. This name has been accepted with less favor by pathologists than by clinicians, for in ordinary hospital material where death has not occurred for a number of days the proximal and distal convoluted tubules may be equally involved, and indeed the changes may be more pronounced in the former. The normal proximal tubule is recognized

by its wider lumen, its larger cells and therefore fewer nuclei, its acidophilic granular cytoplasm, and the brush border of cilia. When the lesions are advanced it may not be possible to distinguish between the two sets of tubules. The lining epithelium is greatly swollen and undergoes complete necrosis. Between the tubules there are collections of inflammatory cells, mainly lymphocytes and plasma cells with occasional polymorphonuclears and eosinophils. Later the necrotic tubules may rupture, their contents become extruded, and a granulomatous type of reaction may develop around them. At this stage the inflammatory and reactive changes may dominate the picture, although these are entirely secondary. Intertubular edema is often a marked and important feature, especially in the boundary zone. Sometimes tubulo-venous lesions may be seen, due to herniation or actual rupture of the tubular contents into a vein with occasional thrombosis, so that blood may pass into the tubules with resulting hematuria. Casts are a prominent feature especially in the boundary zone and medulla. At first these are non-pigmented, but with the passage of time they acquire blood pigment, so that the condition has been given the misleading name of pigment nephrosis. The casts may become overgrown by epithelium, or they may be extruded into the intertubular tissue where they excite a further inflammatory reaction. The condition of the first convoluted tubules varies. The lumen may be filled with epithelial debris, but these tubules are often much dilated and lined by flattened epithelium. This striking dilatation suggests distension of the lumen by urinary secretion which has been unable to pass a barrier in the boundary zone, where the tubules seem to be reduced in number owing to collapse of their walls. The vasa recta of the medulla are greatly congested and dilated, giving an impression of complete stagnation. In contrast to the devastation of the tubules, the glomeruli appear normal.

*Transfusion with incompatible blood* belongs to the anoxic type of nephrosis. When a donor of the wrong group is used for blood transfusion, the patient shows marked hemoglobinuria, and may develop anuria and die of uremia. Hematin casts are found in the renal tubules, apparently depending on acidity of the urine. The presence of blood pigment casts in the tubules is valuable evidence that the blood used in the transfusion was incompatible.

*Crush nephrosis* presents a similar clinical and pathological picture. When a person is buried under a mass of masonry and sustains crushing injuries to the muscles, anuria may develop in the course of a few days, followed by death from uremia. The lesions are those of nephrosis. Pigment casts form a prominent feature. These are said to consist of myohemoglobin (Bywaters).

*Sulphonamide nephritis* is really a nephrosis. Again death is due to anuria and renal failure. In many cases this is due to a state of natural or induced hypersensitivity to the drug (Rich). The general subject of sulphonamide allergy is discussed in Chapter 6. The two striking renal lesions are a nephrotic degeneration of the epithelium of the convoluted tubules and a focal interstitial nephritis (Fig. 320). The anuria may be attributed to the tubular lesions, which are similar to those seen in incompatible blood transfusion and the crush syndrome. It is from the

interstitial lesion that the pathological diagnosis can be made. There are small areas of focal necrosis, associated with which are collections of inflammatory cells, chiefly macrophages, plasma cells, and often large numbers of eosinophils, the latter always suggestive of an allergic lesion.

The *hepato-renal syndrome*, a rather nebulous entity, as Dible puts it, is marked by necrotic cells both in the liver and kidney. There is tubular necrosis with bile staining of the necrotic cells, and focal areas of necrosis in the liver. The condition may develop as the result of crush injuries to the liver and operations on the gall bladder, or in cases of obstructive jaundice which have been subjected to severe abdominal operations. The toxic action of the bile may intensify the necrosis. In the kidney there is a striking absence of the interstitial inflammatory reaction so characteristic of true nephrosis.

**PATHOGENESIS OF ANOXIC NEPHROSIS.**—The mechanism by which the lesions and the anuria are produced has long been a matter of debate.



FIG. 319.—Corrosive sublimate poisoning. Acute calcification of the epithelium of the renal tubules. The two dark masses represent calcified cells.  $\times 300$ .

There seem to be good grounds for believing that the most constant etiological factor is diminution of the renal circulation. For this reason the name of renal anoxia has been suggested for the entire group (Mae-graith *et al.*). When one kidney in the rabbit is removed and the renal artery of the remaining kidney is partially occluded temporarily, changes similar to those of human traumatic uremia are produced (Badenoch and Darmady). The first lesions occur in the loop of Henle, the part of the nephron which is the last to be supplied with blood and therefore most vulnerable to anoxia. Trueta and his associates have suggested that in shock and allied conditions the large efferent arterioles leading into the medulla from the juxta-medullary glomeruli can divert blood from the cortex

and thus produce cortical ischemia. The evidence of this supposed "shunt" was derived from radiography and the injection of dyes into rabbits. Studies comparing renal blood flow with the volume of glomerular filtrate fail to confirm this theory of circulatory diversion, and no evidence has been brought forward to prove that it occurs in man. It is possible that a venous reflux by which the large veins in the medulla become filled may account for the appearance which has been attributed to a shunt.

There can be no question that the renal arteries respond to nervous and possibly hormonal stimuli by vasoconstriction. Reflex anuria, *i. e.*, the complete cessation of urinary output from both kidneys which follows obstruction of one ureter by a calculus, must be attributed to reflex vascu-

lar changes in the other kidney (Cubitt). The same mechanism operates in the shock kidney, the crush syndrome, and apparently in incompatible blood transfusion. The resulting renal ischemia causes necrosis in the tubules farthest removed from the blood supply. From this point onward the key concept, the master word, is increased intrarenal pressure, particularly in the boundary zone. A barrier or road block is built up across



FIG. 320.—Sulphonamide nephritis. Note the focal interstitial nephritis and marked degeneration of tubular epithelium.  $\times 240$ .

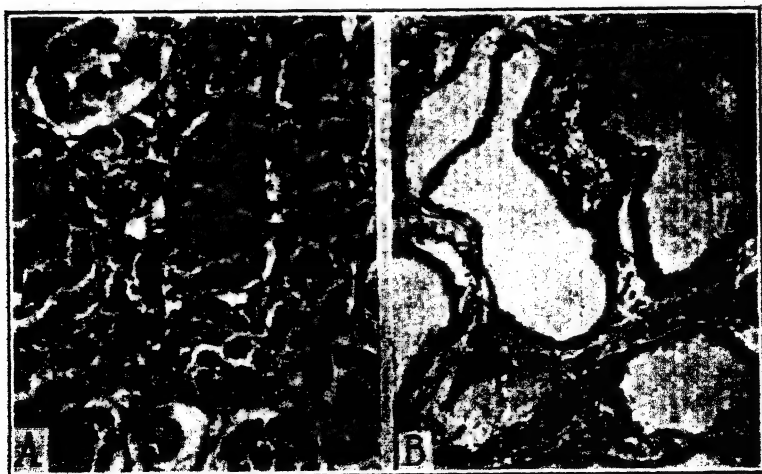


FIG. 321.—Mercuric chloride poisoning. A, early; B, late.  $\times 250$ .

the base of each pyramid which obstructs both the tubules and the thin-walled vessels in the medulla. The chief elements in this block are (1) the interstitial edema due to leakage both from the tubules and blood vessels, (2) the inflammatory exudate which is excited in part by tubular rupture, (3) obstruction of the tubules by swollen epithelium, cellular debris and casts, and, as Barrie points out, (4) spasm of the calyceal muscle and its intrinsic component. Any obstruction increases the exudate from the ruptured tubules, and the exudate in turn still farther increases the intrarenal pressure. Thus a vicious circle is established. The most easily recognized sign of raised intrarenal pressure is the presence of the so-called tubulo-venous thromboses (Barrie, personal communication). These are really herniations of renal substance, into the veins, sometimes with secondary thrombosis. The dilated proximal tubules, the stasis of the vasa recta, and to some extent the anuria may be attributed to the block in which raised intrarenal pressure is so important a factor.

It would be a mistake to think that the whole problem has been solved by the above discussion. The most baffling feature is the anuria, which may develop immediately after an incompatible blood transfusion and be accompanied by sudden pain in the loin. In such a case is the mechanism glomerular or tubular? If the patient dies in a very early stage there may be no visible tubular degeneration nor intertubular exudate. The same is true in experimental ischemia earlier than the second day. It may be that there is an initial and transient glomerular shut down, or some humoral mechanism such as the pituitary antidiuretic hormone may allow fluid to pass through the walls of the tubules and be absorbed without any observable lesion in the tubular walls.

**TOXIC NEPHROSIS.**—Here the problem is much simpler. An exogenous poison such as mercuric chloride (vaginal douching, attempted suicide) or carbon tetrachloride is excreted by the kidney, concentrated in the tubules owing to reabsorption of water, and causes massive necrosis, most marked in the proximal convoluted tubule, the first part to encounter the concentrated poison. Anuria rapidly develops, the non-protein nitrogen in the blood rises, and death may occur from uremia. If the patient does not die at this stage the anuria is followed by diuresis, the first urine being of low specific gravity. When death takes place after two or three days there is seen to be extensive necrosis of the tubular epithelium, the necrotic cells becoming detached and blocking the lumen of the tubules, thus accounting for the anuria (Fig. 321A). Acute calcification of the necrotic cells occurring in the course of a few days is not uncommon (Fig. 319). By the end of a week the tubules may be clear, yet the anuria persists. Apparently the glomerular filtrate escapes back through the bare walls of the tubules into the interstitial tissue, so that none of it reaches the bladder. This mechanism can be watched in the living kidney of the frog poisoned with mercuric chloride (Richards). After the first week the tubules become relined with low, darkly-staining epithelium which is of little use for absorbing water and concentrating the urine (Fig. 321B). The new epithelium gradually develops into a fully formed and functioning lining of the tubules.

**ARTERIOLAR NEPHROSCLEROSIS**

The condition of essential hypertension may be accompanied by degenerative and fibrotic changes in the kidneys. These changes were originally included under the heading chronic interstitial nephritis, but when they came to be differentiated from chronic glomerulonephritis, they were given such names as the hypertensive kidney, the arteriolosclerotic kidney and arteriolar nephrosclerosis. The latter term describes a process, just as do glomerulonephritis and nephrosis, and therefore seems preferable. The condition has long been known as the primary contracted kidney, in contrast to the secondary contracted kidney of glomerulonephritis. Both were originally included under the term granular contracted kidney.

Essential hypertension may continue for twenty or thirty years without evidence of renal involvement, the patient usually dying of one of three causes dependent on the prolonged hypertension: (1) congestive heart failure, (2) coronary sclerosis, (3) cerebral hemorrhage. If he survives these accidents he may gradually develop symptoms of renal insufficiency and finally die of chronic uremia. Such cases are known as benign hypertension and the renal lesions are those of benign nephrosclerosis. In a younger group of patients the hypertension may develop rapidly and pursue an acute and fatal course reckoned in months rather than years. This is the group of malignant hypertension, constituting about 10 per cent of the whole, and the renal lesions are those of malignant nephrosclerosis. The patient may or may not die of acute uremia. From a careful study of the kidney the pathologist should be able to form some opinion as to whether the patient did or did not suffer from essential hypertension, whether the hypertension was of the chronic or the acute type, and if the latter, whether or not death was due to acute renal failure.

The primary renal lesion, which we believe to be the result of the high blood pressure, is arteriolosclerosis (arteriolar sclerosis), causing ischemic atrophy of the glomeruli and tubules resembling that seen in chronic glomerulonephritis. The word arteriole is used in different senses by different workers. It is important to realize this, because it serves to explain the differences in the statistical results of different workers, such for instance as the frequency of renal arteriolosclerosis in hypertension. Some confine it to the afferent and efferent arterioles, whilst others include the distal portions of the interlobular arteries, that is to say, the vessels contained within the true cortex, as contrasted with the interlobular arteries in the medulla. Either system is justifiable, but for the discussion of arteriolosclerosis it is more convenient to use the word arteriole in the wider sense, *i.e.*, as synonymous with small arteries.

Hypertension and nephrosclerosis are not synonymous. Arteriolosclerosis of the afferent arterioles always indicates hypertension, but hypertension may be present without sclerosis of these vessels in 10 per cent of cases before renal insufficiency has developed. If the interlobular arteries and afferent arterioles are taken together, sclerosis is present in 100 per cent of hypertensives, but it is also present in many elderly persons without hypertension. In cases of hypertension with renal failure sclerosis of the afferent arterioles is always present. Benign hypertension and benign nephrosclerosis are therefore not necessarily related, but hypertension acts as an accelerating factor. On the other hand malignant hypertension and malignant nephrosclerosis show a definite correlation, so that malignant nephrosclerosis may be regarded as the renal end-stage of malignant hypertension.



**Benign Nephrosclerosis.**—The *gross appearance* of the kidney depends on the duration and intensity of the vascular lesions. The kidney may appear normal even though there are marked microscopic lesions. Bell and Clawson found smooth kidneys in 75 per cent of cases of essential hypertension, although hyaline arteriolosclerosis was present in 97 per cent. In cases of long standing the kidney may be small, hard, and granular; this is the primary contracted kidney, and it may be greatly shrunken. The surface is covered with little granules produced by an alternation of pale nodules and red depressed portions. The red color is due to atrophy



FIG. 322.—Hyaline thickening of afferent arteriole in nephrosclerosis with great narrowing of the lumen.  $\times 225$ .

of the cortex which allows the underlying vascular tissue to shine through. Small cysts of the surface are common. The cut surface shows irregular atrophy of the cortex and loss or distortion of the cortical vascular markings. The small arteries, especially those at the base of the pyramids, are thick-walled and gape. The gross appearance may closely resemble that of the granular contracted kidney of chronic glomerulonephritis, but in the latter condition the granules on the surface tend to be finer owing to the diffuseness of the lesions, and the arterial lesions are not so evident. Greater shrinkage is possible than in glomerulonephritis, because the remaining glomeruli, being normal, are able to carry on renal function and maintain life. Often the distinction is impossible.

The basic *microscopic lesion* is arterial and arteriolar sclerosis. The vascular changes of hypertension have already been described in detail on page 364. When the hypertension is of gradual development and long continued, the so-called benign

form, two characteristic lesions develop in the renal vessels. These are hyaline degeneration and elastic hyperplasia. Similar changes are found in the arteries of other organs, but not to the same degree nor with the same frequency as in the kidney. *Hyaline degeneration* is best seen in the smallest vessels, such as the afferent and efferent arterioles. It is at first a smooth acidophilic thickening of the subintimal tissue, but in course of time it may involve the entire thickness of the arterial wall, leading to extreme or complete obliteration of the lumen (Fig. 322). Fat is deposited in the degenerated tissue, so that in frozen sections stained with Scarlet Red the arterioles may appear as thick

## PLATE XVII



### Arteriolar Nephrosclerosis.

Thickening and narrowing of the arterioles, atrophy and fibrosis of the glomeruli, degeneration of some tubules, and gradual disappearance of the remainder. One glomerulus is normal, one is shrunken, one is completely fibrosed, and one shows thickening of Bowman's capsule. (Azocarmine.)

red rings. The larger arteries are often the seat of atherosclerosis. *Elastic hyperplasia* or elastosis is most marked in the larger arteries, but some degree of it may be apparent in the arterioles. When the section is stained with an elastic tissue stain it is seen that the internal elastic lamina is split into a number of layers, and the greater part of the thickened intima is composed of elastic fibers, with resulting narrowing of the lumen (Fig. 323). Splitting of the elastica is not seen in an old glomerulonephritis, a point of value in the sometimes difficult task of differentiating that condition from the kidney of hypertension.

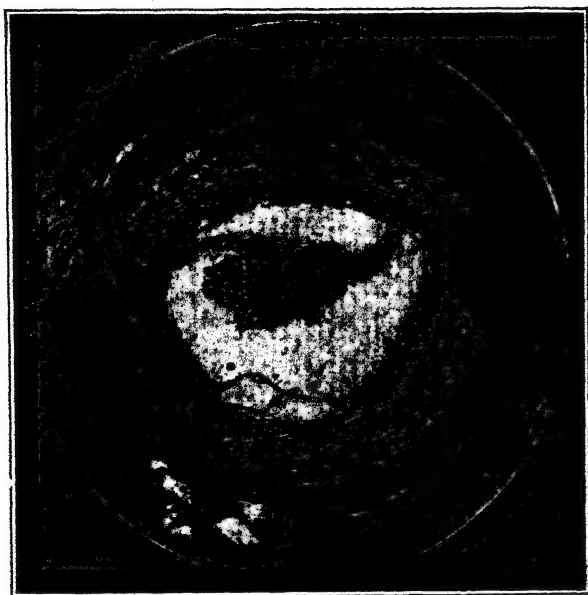


FIG. 323.—Elastic intimal thickening. Marked thickening of the inner coat with reduplication of the internal elastic lamina. (Elastic tissue stain.)  $\times 125$ .

The vascular lesions may remain the only lesions for a considerable time if the lumen of the small arteries and arterioles, the really significant vessels, is not materially narrowed. When such narrowing occurs, ischemic changes follow. Lesions of afferent arterioles affect individual glomeruli whilst lesions of larger vessels affect groups of glomeruli and tubules.

Closure of the arterioles leads to ischemic changes in the glomeruli which they supply. There is great thickening of the basement membrane (best shown by a connective tissue stain), and the entire tuft becomes converted into a hyaline mass (Plate XVII). At the same time the connective tissue of Bowman's capsule becomes markedly thickened, eventually fusing with the hyaline tuft and obliterating the capsular space. The corresponding tubules atrophy owing both to disuse and ischemia.

Closure of the arteries cuts off the blood supply to areas of cortex of varying size, so that wedge-shaped patches of atrophy are seen here and

there (Fig. 324). In these areas both glomeruli and tubules have disappeared, whilst between them the tubules are normal or dilated and the epithelial lining hypertrophied. This hypertrophy and dilatation (compensatory) is especially marked when renal insufficiency has developed, and is always suggestive of that condition. The alternation of atrophic and hypertrophic areas is responsible for the sometimes coarse granularity of the surface.

**Malignant Nephrosclerosis: the Kidney of Malignant Hypertension.**—

In over 90 per cent of cases of essential hypertension there is no serious impairment of renal function, at least for a long time. If the patient escapes death from cerebral hemorrhage or cardiac failure he may eventually die of uremia. In these cases autopsy will reveal very extensive damage to the renal parenchyma, as might be expected. But there is another group of



FIG. 324.—Benign nephrosclerosis, showing a patch of atrophy with dilated tubules on either side.  $\times 60$ .



FIG. 325.—Malignant nephrosclerosis. The surface of the kidney is covered with blotchy hemorrhages.

cases in which at a younger age period (usually in the thirties and forties, sometimes in the twenties) the patient develops an acute and progressive renal insufficiency. The blood pressure is very high, but death is likely to be due to uremia. In some cases the patient dies before the onset of uremia. Hypertensive retinopathy, characterized by edema of the disc and retina and retinal exudates, also serves to distinguish malignant hypertension from benign hypertension with gradual renal failure. The clinical condition is one of malignant hypertension, and the corresponding renal lesions are those of malignant nephrosclerosis.

The *gross appearance* may be sufficiently characteristic to enable a diagnosis to be made with the naked eye. As a rule the kidney is of normal size and may even be enlarged whilst the surface is smooth; the *tempo* of the process has been too fast for atrophy to develop. Sometimes sufficient time has elapsed for it to become contracted and granular. Not infrequently the two kidneys differ markedly in size. The surface may be covered with hemorrhages, usually large and blotchy (Fig. 325), sometimes small and petechial.

Microscopically the significant lesions are again in the vessels, and again they are two in number, namely, cellular hyperplasia and arteriolar necrosis. *Cellular hyperplasia*, also called productive endarteritis and hyperplastic arteriolosclerosis, is the hallmark of rapidly developing hypertension. The walls of the smaller arteries are thickened by a concentric cellular proliferation, so that they may present an "onion-skin" appearance. Fatty degeneration may be marked in frozen sections. Elastic hyperplasia is not

a special feature. *Arteriolar necrosis*, also called necrotizing arteriolitis, is best seen in the afferent arterioles. Nuclear detail is lost, the elastica disappears, the wall stains brightly with eosin, and its limits become indistinct as if red paint had been smudged across it (Fig. 326). Aneurismal dilatation may occur, the necrotic wall is infiltrated with red cells, and hemorrhage is common. Arteriolonecrosis is not nearly so common as productive endarteritis, and its significance is different. It is usually an indication of renal failure, although this is not invariably the case. It appears to be a product of rapid severe hypertension coupled with the action of toxic retention products.



FIG. 326.—Arteriolar necrosis in malignant nephrosclerosis. The afferent arteriole and the right-hand side of the tuft show the smudgy necrotic appearance characteristic of this condition.  $\times 225$ .

The various forms of arterial change may not present the clean-cut picture of a text-book description; thus intimal and medial cellular proliferation may blend so that they cannot be distinguished separately. The important thing is to recognize hyperplastic small arteries and arterioles. In the chronic long-drawn-out cases the characteristic feature is hyalinization; in the more acute and rapid (malignant) forms the small arteries stand out prominently as thick-walled cellular structures with narrowed lumen.

The *renal parenchyma* does not show the advanced atrophy that is seen in the benign form owing to the quickened *tempo*. Two features may often be observed in cases marked by rapid renal failure. These are focal glo-

merulitis and tubular dilatation with hyperplasia of the lining cells. *Focal glomerulitis* is characterized by fusion and necrosis of the capillary loops, swelling, degeneration (fatty, hyaline droplets, or necrosis) of the epithelium covering the tuft, and the formation of fibrinous adhesions between the glomerular loops and the lining of Bowman's capsule. There may be patchy necrosis of the tuft with hemorrhage into the capsular space. *Tubular hyperplasia*, probably compensatory in character, when present in marked degree is excellent evidence of renal failure. It is most marked in chronic glomerulonephritis, is quite pronounced in malignant hypertension, and may be present in lesser degree in benign hypertension if the stage of renal failure is reached.

*Other organs* may show the characteristic hyperplastic arteriolosclerosis and arteriolonecrosis. These are most frequently seen in the fatty capsule of the adrenals or in the glands themselves, but they are also present in the pancreas, retina and brain. In the retina they may be responsible for the lesions of hypertensive retinopathy and in the brain for those of hypertensive encephalopathy.

The main features by which, in characteristic cases, malignant hypertension can be distinguished from the benign form are as follows. In malignant hypertension a relatively young person develops an unusually high blood pressure (over 200 mm. Hg), papilledema is a constant feature, hematuria is common, and death is usually due to acute uremia. The kidneys are of normal size or only moderately contracted, and may show hemorrhages on the surface. The significant microscopic features are cellular hyperplasia, arteriolonecrosis, focal glomerulitis and tubular hyperplasia, the corresponding features in benign hypertension being elastic intimal hyperplasia, hyaline arteriolosclerosis and hyalinization of the glomeruli.

**THE SENILE ARTERIOSCLEROTIC KIDNEY.**—From the pathological point of view this condition might be called senile nephrosclerosis, but it is so many miles away functionally and clinically from true nephrosclerosis (the arteriolosclerotic kidney) that it would be confusing and rather misleading to give it that name. In persons over the age of fifty in whom the aorta and its larger branches show atherosclerosis, the kidneys are often contracted and grossly scarred. The condition might be called the scarred contracted kidney. The scars appear on the surface as depressions and give an impression of old infarcts. If the vascular lesions are more diffuse the kidney may be coarsely granular. The renal artery is markedly atheromatous, with narrowing of the lumen of some of its branches.

The *microscopic picture* corresponds to the gross appearance. Owing to atheromatous narrowing of the larger branches of the renal artery there are wedge-shaped areas of fibrosis where the glomeruli are completely hyalinized, and the tubules have disappeared and been replaced by fibrous tissue. The wedge-shape is caused by the fan-like distribution of the vessels (Fig. 327). The condition has no relation to hypertension, so that the arteriolar lesions characteristic of that state are not seen. The intervening tissue between the sclerotic areas is normal.

**THE RELATION OF SYMPTOMS TO LESIONS IN NEPHROSCLEROSIS.**—In the senile arteriosclerotic kidney there is no hypertension and no renal insufficiency. The kidney is withered and scarred, but, as Clifford Allbutt puts it, it is "a starved but not a corrupt kidney, sufficient for the smaller life of an elderly man." It is not the result of essential hypertension, and as the remaining parenchyma is healthy, there is no danger of renal insufficiency.

In *benign nephrosclerosis* the patient may live for many years with no sign of

renal involvement. Sooner or later there will be a lowering of the specific gravity of the urine, a loss of the concentrating power of the kidney owing to atrophy of the convoluted tubules from loss of their blood supply, and the appearance of small quantities of albumin and occasional granular and hyaline casts. Such a kidney will show sclerosis of many glomeruli and disappearance of the corresponding tubules, but the remaining parenchyma can still be whipped up to perform the work of excretion, as is indicated by hypertrophy of the residual parts, so that there is compensated renal hypofunction but no true insufficiency. If the patient lives long enough the advancing nephrosclerosis will destroy the last remnants of parenchyma and true insufficiency will develop, but as a rule the overstrained vessels of the brain will burst, the laboring heart will suffer defeat, before symptoms of uremia have time to appear.

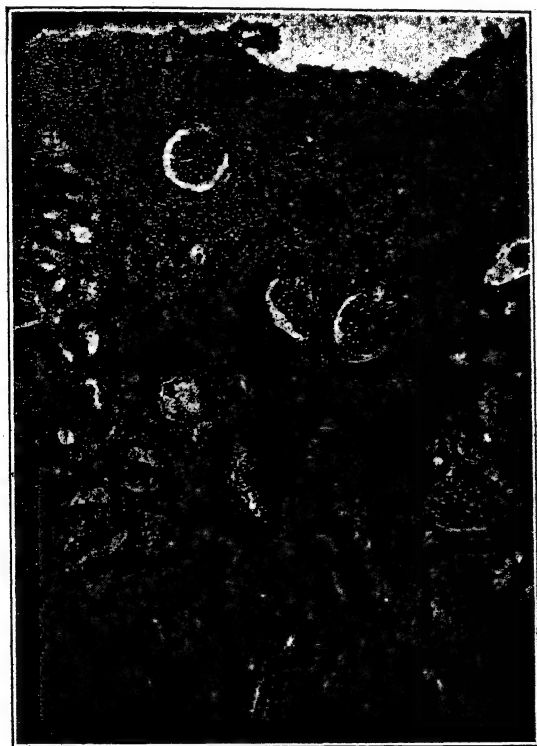


FIG. 327.—Wedge-shaped area of sclerosis in senile arteriosclerotic kidney.  $\times 75$ .

In *malignant nephrosclerosis* the patient may rapidly lose weight. Retinal lesions (edema, hemorrhage and patches of exudate) may be the first indication of the gravity of the condition. It is probable that arteriolar spasm, which may be observed directly in the retinal vessels, is a factor of primary importance in the production of many of the widespread lesions. As has already been pointed out in connection with eclampsia, spasm of an arterial segment is accompanied by dilatation of the segment immediately distal, and through the wall of the dilated segment diapedesis of red blood cells may occur and large quantities of plasma be poured out, giving rise to edema. This is the basis of the retinal lesions, and probably

of the lesions responsible for such symptoms of hypertensive encephalopathy as transient paralysis, convulsions and finally coma. There is soon evidence of renal failure, the concentrating power of the kidney is lost, the specific gravity of the urine falls though never to the extreme low limits of chronic glomerulonephritis, being seldom below 1.010, albuminuria may be marked and casts are constantly present, there may be red blood cells in the urine, the nonprotein nitrogen is retained in the blood, and the patient dies of uremia. These lesions are due to the rapidly produced ischemic lesions of the glomeruli. The presence of the red cells in the urine is explained by the hemorrhage into the capsular spaces, which in turn is due to the necrotic lesions of the glomeruli and afferent arterioles.

THE RELATION OF THE KIDNEY TO HYPERTENSION.—Renal lesions of an ischemic nature may cause hypertension. This is seen in the secondary hypertension which develops in the course of glomerulonephritis. Goldblatt's production of persistent hypertension by means of experimental renal ischemia proves the same thing. Houssay found that transplantation of an ischemic kidney into an animal from which both kidneys had been removed was followed by persistent hypertension. Hypertension of renal origin can be produced by the method of Page, which consists of wrapping the kidney in cellophane. This soon produces a tight-fitting fibrous hull or envelope which compresses the renal parenchyma. Hypertension develops in about four weeks after application of the wrapping, even though the wrapping is unilateral. It is well known that chronic pyelonephritis may be associated with hypertension, and in rare instances only one kidney may be involved, so that nephrectomy is possible. An unusually dramatic case is that reported by MacKay and his associates at the Toronto Western Hospital. A calculus was removed from the kidney of a young man with normal blood pressure. The wound became infected, and four weeks after operation he developed very severe cerebral symptoms and marked hypertension (200/140 mm. of mercury). A second operation showed the kidney to be surrounded and compressed by a tight-fitting hull of fibrous tissue. When this was removed the symptoms promptly disappeared, and the blood pressure returned to normal where it has remained for a number of years.

The renal pressor substance, renin, appears to be contained in the proximal convoluted tubules, not in the distal tubules nor in the juxtaglomerular group of cells (Friedman and Kaplan). Differentiation between the two groups of tubules can be accomplished by injection of sodium tartrate, which produces necrosis of the proximal but not of the distal tubular epithelium.

The presence of ischemic renal tissue is not necessary for the production of hypertension. Grollman and his associates have kept dogs with bilateral nephrectomy alive for ten weeks by means of the artificial kidney. These animals developed the clinical picture of hypertensive cardiovascular disease and the arterial lesions of malignant hypertension. Any theory relating to the pathogenesis of hypertension must take into account the fact that hypertension and arteriolar sclerosis may occur experimentally in the absence of renal tissue, and that the presence of renal tissue appears to be protective against these two conditions. The distinction between the renal hypertension of glomerulonephritis and primary hypertension may be easy for the clinician if the patient has been under observation for a considerable period. In the primary form high blood pressure develops early, whilst renal insufficiency is a late manifestation. Papilledema (in the malignant form), cerebral hemorrhage, coronary heart disease, and congestive heart failure are common features. In glomerulonephritis hypertension develops gradually *pari passu* with renal insufficiency, and marked secondary anemia is an early feature. If the patient is seen only after uremia has developed it may be very difficult to make the distinction.



The pathological distinction may be easy or difficult. In nephrosclerosis the lesions are much more patchy than in glomerulonephritis, and the remaining glomeruli are unaffected. Epithelial crescents, which may be fibrosed, indicate glomerulonephritis. The arterial lesions of nephrosclerosis, both benign and malignant, are characteristic. A serious difficulty is presented by the fact that hypertension in the uremic stage of glomerulonephritis may cause vascular lesions identical with those of malignant nephrosclerosis. In both diseases a vicious circle may be established. Hypertension leads to arteriolosclerosis, this produces ischemic lesions, and these in turn may intensify the hypertension. This is true also of chronic pyelonephritis.

It is evident that renal lesions can produce hypertension. The mystery of essential or primary hypertension, however, still remains unsolved. Goldblatt has produced a condition apparently identical with essential hypertension in the dog by means of bilateral experimental ischemic lesions of the kidneys. The success of Wilson and Byrom with the rat is even more significant, for by means of unilateral renal ischemia they were able to produce persistent hypertension together with the lesions of malignant nephrosclerosis in the other kidney, a condition which progressed even after the ischemic kidney was excised. Against this imposing mass of experimental evidence is the fact that a person may have benign hypertension without vascular renal lesions other than those incidental to any person of the same age. Even if specific vascular lesions are present there may be little or no vascular occlusion with consequent renal damage. In view of the vast bulk of normal kidney tissue remaining it does not seem likely that any minimal lesions which may be present could produce so striking a change in the blood pressure. It is improbable that primary renal vascular disease is a common cause of hypertension in man. The kidney is the victim rather than the culprit. It appears more probable that essential hypertension is due to an unknown extra-renal factor, but that in the later stages a renal component (ischemia) plays a part as the vicious circle develops. It is possible that studies on the juxtaglomerular apparatus may throw further light on the problem.

**MULTIPLE MYELOMA.**—In this widespread disease of bone the patient may develop anuria and die of uremia. At autopsy the renal glomeruli are normal, but the tubules are either atrophied or filled with peculiarly dense firm casts, which may excite a foreign body giant-cell reaction (Fig. 328). In this disease the urine may contain a peculiar form of protein known as Bence-Jones protein, and it is this which forms the casts. The tubular atrophy is caused by obstruction. Apparently the uremia has an obstructive basis.



FIG. 328.—Kidney in multiple myeloma; cast with giant cells.  $\times 150$ .

**RENAL OSTEODYSTROPHY.**—In this condition, known also as renal infantilism and renal dwarfism, there is an association of hypoplasia and fibrosis of the kidneys in children with defective growth and changes in the bones. In all cases there is dwarfism, and infantilism when the patient reaches puberty, but in only about two-thirds of the cases do the bone lesions develop. These lesions are osteoporosis, extensive deformities at the epiphyses, and bowing of the shafts. To these changes the name of *renal rickets* is often applied. They are supposed to be due to the renal insufficiency, which results in retention of phosphorus, upset of the calcium-phosphorus ratio, and acidosis. Decalcification occurs in the presence of acidosis and phosphorus retention. The essential defect is inability to excrete phosphorus. The blood may show marked lipemia and some nitrogen retention, but the blood calcium is said to be normal. Sometimes hypertension is present. The kidneys are contracted and fibrosed, and show marked arteriosclerosis. It is probable that the common cause of the contracted kidney is pyelonephritis in early childhood. It is possible, however, that in some cases the primary defect may be endocrine (parathyroid or pituitary) rather than renal in origin, in which case the renal lesions must be regarded as secondary. Price and Davie after weighing the two views define the condition as "a disease of childhood characterized by skeletal demineralization with resultant deformities, and associated with chronic renal disease which in uncomplicated cases terminates in uremia." The final result may be the same from whichever end one starts.

### OTHER FORMS OF NEPHRITIS

**Thrombotic Glomerulonephritis.**—This condition has been known in the past as embolic glomerulonephritis, in the belief that the nephritic lesions were due to minute emboli from the vegetations of subacute bacterial endocarditis. This is not correct. It is true that the commonest lesions are infarcts produced by emboli occluding the larger vessels. Scattered over the surface there may be great numbers of small red spots, giving it the name of the "flea-bitten kidney." These represent small hemorrhages into the glomerular spaces. The glomerular lesions may be diffuse or focal. The chief diffuse lesions are proliferation of the capillary endothelium, so that the tuft has a more cellular appearance than normal, and thickening of the capillary basement membrane. The focal lesions are less common, but are much more striking, and indeed are pathognomonic. The lesion takes the form of a patch of coagulation necrosis in the tuft which is readily recognized (Fig. 329). The lumen of the glomerular capillaries is filled with hyaline thrombi, similar to the material which blocks the vessels in acute glomerulonephritis (Bell).

Hemorrhage takes place into the glomerular space owing to necrosis of the capillary loops, but the blood is more readily seen in the tubules than in the space, for it is washed out by the flow of urine. If the necrotic part of the tuft comes in contact with the capsule there may be a localized proliferation of the capsular epithelium with the formation of a kind of epithelial crescent. Or adhesions may form between the tuft and capsule. If the patient lives long enough there will be healing and fibrosis.

The only *symptom* is the presence of red blood cells in the urine. As so few glomeruli are involved there is no danger of renal insufficiency. In the exceptional case which may die of uremia it will be found that a true diffuse glomerulonephritis has been added.

**FOCAL NEPHRITIS.**—The glomerulonephritis of Bright's disease is diffuse. There may also be a focal nephritis; (focal suppurative nephritis, *i.e.*, multiple embolic abscesses, is not considered here). The condition is usually called focal glomerulonephritis, but it differs so fundamentally from glomerulonephritis that it seems better to call it focal nephritis, thereby avoiding confusion. It complicates an acute infection, usually tonsillitis or streptococcal sore throat. It is probable that many cases of so-called "*essential hematuria*" are really examples of mild focal nephritis.

The *kidney* shows small hemorrhages on the surface, and on the cut surface the glomeruli appear as red points. *Microscopically* the chief lesion is hemorrhage into the capsular space of many of the glomeruli. This explains the constant presence of blood in the urine. The great bulk of the parenchyma is untouched, so that there is no renal failure, no hypertension and no edema.



FIG. 329.—Glomerular lesion in subacute bacterial endocarditis. The upper part of the tuft is completely necrotic.  $\times 300$ .

**ACUTE INTERSTITIAL NEPHRITIS.**—This rare condition bears no relation to the other forms of nephritis. It occurs as a complication of the acute infectious fevers, especially scarlet fever and diphtheria. There is an acute inflammation of the interstitial tissue which is packed with lymphocytes, plasma cells, and a few polymorphonuclears. Yet the glomeruli and tubules remain intact. Kimmelstiel believes that the condition represents an allergic reaction to foreign proteins rather than a bacterial infection. As the glomeruli and tubules are not invaded there is no renal insufficiency so that the cases seldom come to autopsy. The urine merely shows a little albumin and a few lymphocytes and red blood cells.

## SUPPURATIVE INFECTIONS OF THE KIDNEY

Suppuration of the kidney is caused by the pyogenic bacteria, in particular *B. coli*, *Staphylococci* and *Streptococci*. Infection may be

hematogenous or from below. Urinary stasis from whatever cause is liable to be followed by ascending infection from the bladder to the kidneys, probably by way of the lymphatics.

**The Pyemic Kidney.**—This is merely a renal manifestation of a general pyemia. Owing to a widespread blood infection pyemic abscesses are formed in various organs, including the kidneys. The infecting agent is usually *Staphylococcus aureus* or *Streptococcus hemolyticus*. The condition is a common complication of acute osteomyelitis, carbuncle, ulcerative endocarditis, and puerperal sepsis. When staphylococci are injected into the blood stream of a rabbit they are arrested by the glomeruli and produce multiple small abscesses. Small yellow abscesses surrounded by a red zone are scattered over the surface and throughout the substance of

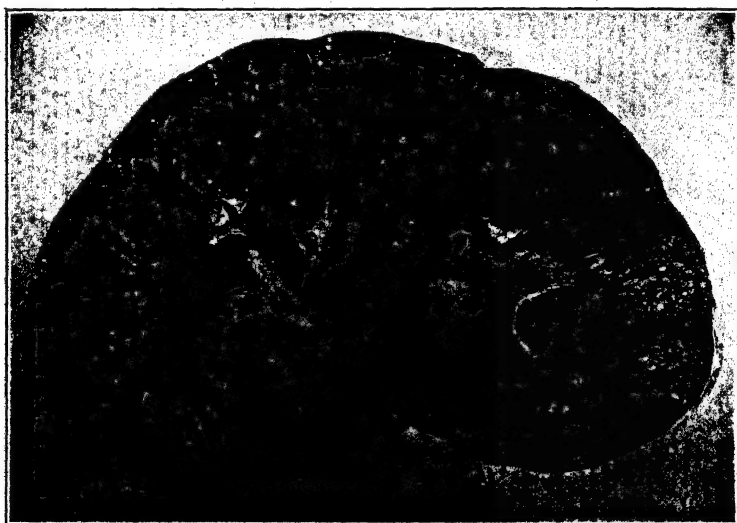


FIG. 330.—The pyemic kidney. Pyemic abscesses are scattered diffusely through both cortex and medulla.

both kidneys (Fig. 330). *Microscopically* they consist of circumscribed collections of polymorphonuclears, and often contain masses of cocci. The condition is a terminal one, and the patient dies of septicemia before there is time for any marked degree of renal destruction.

**Pyelonephritis.**—Pyelonephritis is an interstitial inflammation of the kidney, and bacteria can be demonstrated in the tissues. This is in contrast to glomerulonephritis which is a disease of the nephrons in which no bacteria can be found. The term signifies inflammation of the kidney and renal pelvis. The renal infection may be hematogenous in origin, or it may ascend from below. An ascending infection is particularly common in infancy, pregnancy, and over the age of fifty due to prostatic enlargement in the male and cancer of the cervix in the female. Pyelitis in children occurs in girls, not in boys, the infection coming from the vagina. In autopsy material the obstructive form is 12 times as common as the non-

obstructive (Bell). Low obstruction (below the bladder) is more important than high obstruction (above the bladder). *Bacillus coli* is the common infecting organism, but the pyogenic cocci are frequent in hematogenous infections. The element of obstruction is of the greatest importance in determining the outcome. G. K. Mallory and his co-workers showed this by injecting colon bacilli intravenously into rabbits in which one ureter had been partially ligated; acute pyelonephritis developed in the obstructed kidney in 75 per cent of the animals, but never in the unobstructed kidney. Release of the obstruction after a few days induced healing of the pyelonephritic process. In man the question of whether a blood infection will cause unilateral or bilateral renal lesions is probably largely dependent on the presence or absence of obstruction. In ascending infection some element of obstruction in the urinary tract is likely to be present from the beginning. The lymphatics from the kidney drain directly into the thoracic duct, often with no intervening lymph nodes, so that infective material may reach the blood stream in quantity and give rise to pyrexia and chills.

The *gross appearance* varies extremely with the stage of the disease. As a rule both kidneys are involved, but the lesions are often much less advanced in one than in the other. They may be focal or diffuse. In the acute stage the kidney is swollen and congested, and the pelvis is of a bright red color and filled with pus. Under the capsule there are numerous yellow spots representing areas of suppuration, as well as dark irregular patches which form the base of wedge-shaped areas in the renal substance. The superficial lesions are often raised above the surface as small pustules. If healing occurs later they are represented by depressed U-shaped scars. The cut surface shows patchy areas of suppuration which tend to be spherical in the cortex and linear in the pyramids. If suppuration is progressive, abscess cavities are formed with gradual destruction of renal tissue. The outline of the calyces is destroyed, and the resulting distortion seen in the x-ray film is an important feature in the clinical diagnosis. When obstruction is marked from the beginning the element of hydronephrosis enters the picture, hydronephrotic atrophy leading to destruction of the medulla and much of the cortex. The kidney becomes converted into a bag of pus, a condition known as *pyonephrosis*. A pure hydronephrosis in an advanced stage may become infected. Such a kidney is much enlarged, the surface irregularly lobulated, and when it is opened it presents a picture of pyonephrosis in which a mere shell of kidney tissue is left.

The disease may develop in a more gradual and insidious manner with little frank suppuration. The inflammation, which is chronic in character, extends here and there in the kidney, destroying renal tissue, but being followed later by healing, fibrosis, and contraction. The result is a contracted kidney, on the surface of which there are depressed scars. If these scars are of considerable size they are apt to be regarded as healed infarcts. When they are much smaller the effect is to give the kidney a granular appearance which may be hard to distinguish from that of chronic glomerulonephritis or arteriolar nephrosclerosis. This condition is called *pyelonephritic contracted kidney*, and in the past it has frequently been mistaken for the two diseases just mentioned. Chronic and healed pyelonephritis is a much commoner condition than used to be supposed. Weiss and Parker

in their classic paper found it to be a more frequent cause of contracted kidney than glomerulonephritis. The surface of the kidney is finely granular in glomerulonephritis, more coarsely scarred in chronic pyelonephritis. The scars of nephrosclerosis are pale and on the cut surface are V-shaped like those of healed infarcts. The scars of pyelonephritis tend to be dark (due to vascularity) and saddle-shaped on the outer surface and U-shaped on the cut surface. In distinguishing between chronic pyelonephritis and other conditions with which it may be confused, attention should be paid to the renal pelvis (thickened), calyces, and ureter.

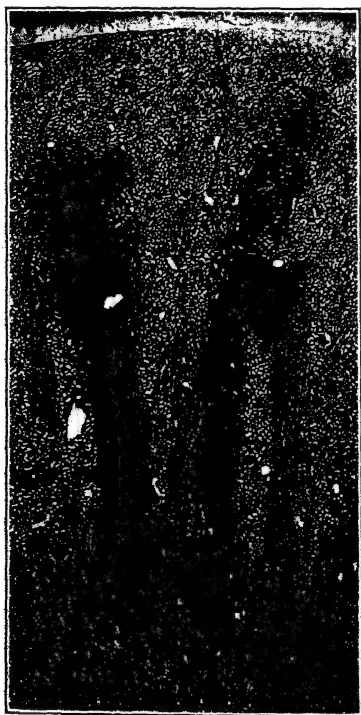


FIG. 331.—Pyelonephritis. The linear circumscribed lesions involve both cortex and medulla.

The *microscopic picture* varies with the stage as much as does the gross appearance. There may be many small abscesses and widespread interstitial infiltration with polymorphonuclear leucocytes. Much more usual, however, is a streaky linear round-cell infiltration with an admixture of polymorphonuclears (Fig. 331). In both cases there is destruction of the renal tubules, with gradual replacement by scar tissue which is more abundant and dense than in nephrosclerosis. Many tubules are filled with pus cells. The process is characteristically patchy, and in the chronic cases the tubules in the intervening areas are either normal or dilated. A striking feature, especially in the scarred areas, is the presence of dilated tubules lined by flattened epithelium, and filled with dense, acidophilic colloid-like material, so that in places the tissue may resemble the thyroid gland. Periglomerular fibrosis is a marked feature even when the glomeruli are intact. In the renal pelvis there is round-cell infiltration or fibrosis, a

valuable diagnostic feature for the pathologist in quiescent cases. The arteries in the affected areas show endarteritis obliterans, such as may occur in any area of chronic inflammation. Much of the arterial thickening represents disuse atrophy; it is an adjustment of the lumen to the decreased blood flow.

The *clinical picture* will naturally depend on the stage of the disease. In acute cases there is pain and tenderness over the kidneys, fever, leucocytes and pyuria. In chronic cases with extensive scarring the symptoms will be those of contracted kidney due to other causes, those, namely, of renal failure with or without hyper-

## PLATE XVIII



### *Papillitis Necroticans.*

Several of the pyramids as well as the papillæ are yellow and necrotic.  
From a case of diabetes mellitus.

tension. The hypertension is presumably due to renal ischemia, but the matter is not quite so simple as it seems, for of two patients with equally ischemic kidneys one may have marked hypertension whilst in the other the blood pressure is normal. In the pyelonephritis which is so common after the age of fifty, hypertension is a frequent accompaniment, but as both conditions are common at this period the element of coincidence cannot be eliminated. In the pyelonephritis of childhood, the late stage of which was first recognized by Longcope, this element does not need to be considered. In some of these cases hypertension has developed a number of years after the onset of the disease.



FIG. 332.—Papillitis necroticans.  $\times 15$ .

**PAPILLITIS NECROTICANS.**—Necrotizing papillitis is an uncommon but serious condition, for when bilateral it usually gives rise to acute and fatal renal failure. A number of papillæ are soft and yellowish, and because of their strategic position the ducts of Bellini are obstructed. The necrotic lesion resembles an infarct, pale yellow in color with a red border of inflammatory reaction (Plate XVIII and Fig. 332). The condition may occur as a complication of diabetes or as a result of ureteral obstruction. In the diabetic cases there is first a pyelonephritis due to the predisposition of diabetics to infection, and the interstitial inflammation leads to pressure necrosis of the papillæ. In non-diabetic persons with urinary obstruction this order is reversed; increased pressure leads to ischemic necrosis of the papillæ, with pyelonephritis as a secondary event. This belief is supported by the fact that experimental ligation of the ureter may result in necrosis of the renal papillæ (Muirhead *et al*).

**PERINEPHRITIC ABSCESS.**—This condition, also called perirenal abscess, is a localized suppuration in the perirenal tissue, usually due to *Staphylococcus aureus* from a boil or carbuncle in the skin. Occasionally a pyelonephritis or a small localized focus of suppuration in the kidney is the evident source of infection, but in most cases the perirenal lesion has the appearance of being primary. As the result of experimental work on hematogenous infection in animals it is known that staphylococci may produce a minute lesion in the renal cortex, and then pass along



cortical lymphatics through the capsule to the perirenal tissue. This is what probably happens in man, and an abscess is produced, usually behind the kidney.

A *carbuncle of the kidney* is also a localized hematogenous staphylococcal infection. A large necrotic area containing several foci of suppuration is separated from the rest of the kidney by a broad zone of granulation tissue. Ball and Evans' book contains a beautiful picture of the lesion. A remarkable feature is the relative freedom of the urine from pus. This may be explained by the destruction of the tubules in the lesion itself, and the intact condition of the glomerulo-tubular units at the periphery.

## TUBERCULOSIS OF THE KIDNEY

Tuberculosis of kidney occurs in two forms: (1) acute miliary tuberculosis, and (2) chronic tuberculosis. *Miliary tuberculosis* is merely part of a general miliary infection, and is a postmortem finding. The kidney is studded with miliary tubercles, which on the surface may be mistaken for the abscesses of a pyemic kidney, but they show no border of congestion.

*Chronic tuberculosis*, also known as *ulcero-caseous tuberculosis* and *surgical tuberculosis*, is at first a local condition. The primary lesion is often in bone. The bacilli are carried to the kidney by the blood. It used to be believed that tubercle bacilli could be excreted by healthy kidneys (excretory bacilluria). This is wrong. A lesion is always present in the kidney, although serial sections may be needed to demonstrate it. Band points out that the earliest lesions occur in the cortex in relation to the glomeruli, although they may only be seen in microscopic sections (he examined 2,000 sections from each half kidney). These minute primary lesions often heal. They may ulcerate into the tubules, and as the collecting tubules converge at the apex of the pyramids it is natural that secondary lesions should develop there. These are the first lesions which are readily visible to the naked eye. Ulceration of the calyces now occurs, and in the x-ray picture (pyelogram) a characteristic distortion of the outline of the calyces and pelvis can be detected, which may allow a remarkably early diagnosis to be made.

The lesion at the apex of the pyramid is at first a localized nodule, but infection spreads up the lymphatics along the line of the collecting tubules, as well as down into the pelvis. In this way a *tuberculous pyelonephritis* is produced. In the tuberculous form there is a much greater tendency to destruction (*renal phthisis*), and large cavities with rough ragged walls are produced containing thick creamy odorless pus which is sterile on culture unless secondary infection has occurred. These communicate with the pelvis, so that a large amount of pus appears in the urine. The condition is now a *tuberculous pyonephrosis* (Fig. 333). Caseation, softening, and liquefaction may eventually lead to destruction of the entire kidney. The kidney may be considerably enlarged or may become shrunken. Much depends on whether tuberculous stricture of the ureter occurs. Such a stricture may prevent the pus from reaching the bladder, and thus mask the true nature of the condition. In the shrunken kidney the pus becomes inspissated and converted into a putty-like material in which lime salts may be deposited. In the roentgenogram these deposits may give an outline of the calcareo-caseous sac representing the kidney or merely spotty

shadows. The *microscopic appearance* is that of tuberculosis in its various stages (Fig. 334).

**SPREAD.**—The spread of the disease is of great importance. At first localized, the infection spreads very readily in the connective tissue of the submucosa of the renal pelvis. Infection spreads to the *ureter* with the formation of tubercles and tuberculous granulation tissue in the mucosa and ulceration of the surface. The chief lesions are in the upper and lower thirds. A stricture may develop, but more often the ureter is converted into a rigid, thickened, dilated tube. The *bladder* is infected early, and the chief symptoms—pain and frequency of micturition—are due to this infection. It begins at the opening of the ureter, where hyperemia and



FIG. 333.—Tuberculous pyonephrosis. In the cortex of the lower part there are solid caseous areas; further up cavity formation has taken place; the ureter is considerably thickened.



FIG. 334.—Renal tuberculosis.  $\times 100$ .

tubercles can be seen with the cystoscope and an early diagnosis established in this way. The infection spreads along the submucosa of the trigone, causing ulceration of the overlying mucous membrane. It may extend to the prostate and seminal vesicles, and along the vas deferens to the epididymis, thus producing a *genito-urinary tuberculosis*. There is a remarkable tendency for the bladder lesions to heal, and removal of the kidney may be followed by complete recovery. The *other kidney* becomes infected sooner or later, so that at autopsy the condition is always bi-

lateral, though much more marked on one side than the other. This involvement is probably due to an ascending infection from the bladder.

**THE RELATION OF SYMPTOMS TO LESIONS.**—The two chief symptoms are frequency of micturition and blood in the urine. These are early as well as common symptoms. The frequency is vesical and the hematuria renal in origin. The frequency, which is often associated with pain on urination, is due to lesions in the sensitive trigone of the bladder. It becomes more marked as the capacity of the bladder diminishes. There is often an associated *polyuria*. Renal pain is not an early or a prominent symptom, although there may be an aching in the loin aggravated by jolting. *Renal colic* may be caused by the release of blood along the ureter. The *hematuria* is caused by destruction of vessels in the renal calyces. *Pus in the urine* is a later development, depending on the amount of caseation and liquefaction. It is seldom as abundant as in pyelonephritis and pyonephrosis. Tubercle bacilli may be found with the microscope, or culture and guinea-pig inoculation may be necessary. There are usually no ordinary pyogenic bacteria. Death is usually due to uremia from renal failure, sometimes to general miliary tuberculosis.



FIG. 335.—Polycystic kidney. The kidney is enlarged and converted into a series of cysts containing thick material which has been coagulated by the fixative.

### CYSTS OF THE KIDNEY

**Polycystic Kidney.—Congenital Cystic Kidney.**—This condition is found once in every 500 autopsies (Bell). It is nearly always bilateral, but in about 5 per cent of cases may be unilateral. There are two periods of life at which it is found. About 30 per cent occur in infants, the majority still-born. The remaining cases present symptoms in early adult and middle life. The progressive atrophy of the parenchyma caused by continuous dilatation of the cysts is balanced during youth by compensatory hypertrophy, but by the third decade this compensatory power is lost. The kidneys may be enormously enlarged or only slightly so. They are converted into a series of cysts, which may occasionally communicate with one another but never with the renal pelvis (Fig. 335). The surface is grossly nodular owing to the large cysts. The contents may be thin or thick and viscid, clear amber or dark brown from hemorrhage, and sometimes contain urea. Hardly any renal tissue may be left, so that the occur-

rence of hypertension, renal insufficiency, and uremia is easily understood. Infection of the cysts is not uncommon. *Microscopically* the cysts are lined by cubical epithelium, but in the large cysts it may be flattened. The remaining kidney tissue shows marked evidence of nephrosclerosis, with fibrosis of the glomeruli and disappearance of the tubules. Ritter and Baehr point out that gross study of injected kidneys shows that the interlobar and interlobular arteries lie mainly in the cyst walls, often just under the lining epithelium. These vessels are easily ruptured as the result of hypertension or slight trauma, so that the cysts frequently contain fresh



FIG. 336.—Large solitary cyst of the kidney.

or old blood, and the patient suffers from attacks of lumbar pain. If the hemorrhage into a cyst should cause rupture into one of the calyces there will be hematuria—a not uncommon symptom. When the kidney is injected with an opaque substance and roentgen-rayed, there is found to be a great disappearance of vessels and occlusion of the arterial tree.

The congenital nature of the condition is suggested by the occasional occurrence of other congenital anomalies. Small cysts are sometimes present in the liver (due to malformation of the bile ducts), and more rarely in the pancreas. There is, moreover, a strong hereditary tendency. It used to be supposed that the cysts were due to failure of the convoluted tubules to fuse with the collecting ones, but it is more probable, as Kampmeier points out, that the cystic condition is merely a persistence of one stage of renal development. In the early embryo the convoluted tubules which first develop in connection with the collecting tubules are not per-

manent, but become detached and persist for a time as cystic structures. Normally these fetal cysts atrophy. If they persist they form a cystic kidney. Clinically it is justifiable to speak of a surgical and a medical type (but not with respect to treatment). In the surgical type the symptoms such as pain, tumor, and hematuria, are referable to one kidney. In the medical type there are symptoms of acute or chronic renal insufficiency, with arterial hypertension in over 50 per cent of the cases.

**Solitary Cyst.**—Sometimes a large single cyst is found projecting from one pole of the kidney, which may cause a degree of enlargement that can be detected clinically (Fig. 336). Some of these cysts may attain a very large size. There may be more than one of these "solitary" cysts. Often the cyst is quite small. The contents are serous and rarely contain urea. Hemorrhage may occur into the cyst. These cysts are rarely found in infants and children, a fact suggesting that they are acquired rather than congenital.

## TUMORS OF THE KIDNEY

There is no more perplexing chapter in the whole of pathology than that which deals with tumors of the kidney. Endless varieties have been described, but nearly all the malignant tumors of the kidney appear to be variants of two main types, and these alone will be considered here. For details of the variations the reader is referred to special treatises on tumors. The main types are the hypernephroma (Grawitz's tumor) and the embryoma (Wilms' tumor).

**Hypernephroma.**—This tumor owes its common name to the original suggestion of Grawitz, in 1883, that it was derived from rests or remnants of adrenal cortex which had been included in the kidney. For long this was the popular view, but it must be given up, for there is no doubt that the tumor is a renal carcinoma arising either from adult tubules or, as suggested by Wilson in 1910, from islets of nephrogenic tissue which have persisted in the renal cortex, thus bringing it into line with the embryoma (see below). Such developmental rests are common in infants though rare in adults, thus illustrating the general law of tumor growth that persisting undeveloped embryonic tissue diminishes as age increases, but the incidence of malignant tumors derived from it increases. The chief argument in favor of the original Grawitz view is that the tumor is often composed of clear, vacuolated, lipid-filled cells similar to those of the adrenal cortex, but similar clear cells are found in adenomas of the kidney composed of typical tubules. The hypernephroma may show a tubular formation which is never seen in the adrenal gland or tumors of the adrenal cortex. The latter tumors are associated with sex disturbances (virilism) which are constantly absent in hypernephroma. Leary suggests that an accumulation of crystalline cholesterol ester in the cells of a benign cortical adenoma may act as a carcinogen which starts the formation of an adenocarcinoma or hypernephroma. He also thinks that it is the stimulating agent responsible for benign cortical adenomas. There is no doubt that this lipid is readily deposited in the renal epithelium, and that it is related chemically to such carcinogens as methylcholanthrene.

The *gross appearance* is so characteristic that it can usually be recognized at a glance (Fig. 337). The tumor forms a rounded mass usually in the upper or lower pole, which may attain a large size. At first it appears encapsulated, but later is invasive. The great characteristic of the cut surface is its variegated appearance. Yellow is the chief color (due to lipid), but there are also red hemorrhagic areas and cysts of varying size, while only a small piece of normal kidney tissue may be left. Some of the cysts contain serous or mucinous fluid, but others represent areas of necrosis into which hemorrhage has occurred. There may be a fibrous core in the center of the tumor.

The *microscopic picture* may be as varied as the gross appearance. The tumor cells are usually very characteristic, being large and rounded with a peculiarly clear or vacuolated cytoplasm (Fig. 338). The clearness or vacuolation is due to the presence of a large amount of lipid (mostly cholesterol ester), and in part to the presence of glycogen, shown by Best's carmine stain after alcohol fixation. Occasionally the tumor is composed of dark granular cells; this granular-cell form is much more malignant.



FIG. 337.—Hypernephroma. The cut surface has a variegated appearance.



FIG. 338.—Microscopic appearance of a hypernephroma. The clear cells show a very marked alveolar arrangement.  $\times 200$ .

The arrangement of the cells is also variable. There are three possibilities, which in their order of frequency are: (1) a cystic papillary formation, in which papillary processes project into indefinite cystic spaces, but with no real tubular formation; (2) an alveolar arrangement of solid cords, divided into masses by thin septa; (3) occasionally a definitely tubular arrangement which irresistibly suggests that the tumor is of renal origin. The stroma is scanty, but the blood vessels form a striking feature of the picture; they are usually numerous and very large, and the vessel wall often seems to be formed of tumor cells, thus accounting for the frequent hemorrhage into the tumor and the tendency to metastasize by the blood stream.

**SPREAD.**—The tumor may remain silent for a long time, and metastases are often the first evidence of a renal tumor. At first the tumor is sharply separated from the kidney by a fibrous capsule, but sooner or later the malignant character becomes obvious, the capsule gives way, and the kidney is invaded. There is a special tendency to invasion of veins, and the tumor may grow into the renal vein and even into the inferior vena cava, with widespread metastases as the result. The lungs and bones are involved most often, but the liver often shows metastases, and the regional lymph nodes are invaded *via* the lymphatics. In the lungs the metastases show a curiously clear-cut outline in the roentgen-ray picture known as the "cannon-ball" appearance. Hypernephroma is one of the most important causes of secondary tumors of bone, and the first manifestation that there is anything wrong with the patient may be the occurrence of a spontaneous fracture. A curious feature is that in 60 per cent of the cases there is a solitary bone metastasis. The order of frequency of involvement is upper end of humerus, spine, femur, pelvis, and ribs.

**THE RELATION OF SYMPTOMS TO LESIONS.**—Of the symptoms painless hematuria is by far the most important, and it occurs fairly early in over 50 per cent of the cases. It is accounted for by the numerous large thin-walled blood spaces, which readily rupture into the renal tubules. Pain is uncommon, and a tumor can be felt only late in the disease. The tumor causes deformity of one or more of the calyces of the renal pelvis at an early stage, and this may be detected in a pyelogram. Long-continued fever is a remarkable feature of some cases; it is probably a protein fever due to breaking-down of tissue. A pyelogram (roentgen-ray of pelvis) shows the following: (1) spider distortion due to stretching of the calyces, (2) filling defects in the pelvis, and (3) displacement of the ureter outwards. In embryoma, on the other hand, the pyelogram shadow is displaced by the tumor but not otherwise altered until late, when the renal pelvis is invaded. The *prognosis* is bad owing to the tendency to blood spread, but early removal may be followed by cure.

**Embryoma, Wilms' Tumor.**—This is the commonest abdominal malignant tumor of early childhood. It usually occurs during the first three years of life and after the age of five years it is infrequent, but it may very rarely occur in adults. It may attain an enormous size, nearly filling the abdomen. Quite frequently it is bilateral. The diagnosis cannot be made until a tumor appears, for there is no hematuria and no pain, because the renal pelvis is not invaded. Intravenous urography may show a complete absence of the normal roentgenogram shadow or distortion of the calyces.

Fever occurs in 50 per cent of the cases. There is a marked response in the size of the tumor to radiation, a useful diagnostic point.

The tumor, which commences in the cortex, is gray, soft, and has the homogeneous character of a sarcoma (Fig. 339), but necrosis and hemorrhage may alter this appearance. It tends to destroy the whole kidney, and may spread to neighboring organs, but distant metastases by the blood stream are not frequent. In this respect it differs completely from hypernephroma. The *microscopic appearance* varies in different cases and in different parts of the same tumor. The general character is sarcomatous, and in the past the Wilms' tumor has been classed as "sarcoma of the kidney in children." The cells may be round or fusiform. Glandular (tubular) elements are often present, and such tumors have often been called *adenosarcoma* (Fig. 340). Smooth muscle and striated muscle are not uncommon, and in rare cases there may be cartilage and bone. The tumor is markedly radio-sensitive.

The Wilms' tumor is a developmental tumor, and is best called an embryoma or an embryonal mixed tumor. It may seem strange that an epithelial organ such as the kidney should give rise to a developmental tumor with connective-tissue (sarcomatous) characteristics. This is

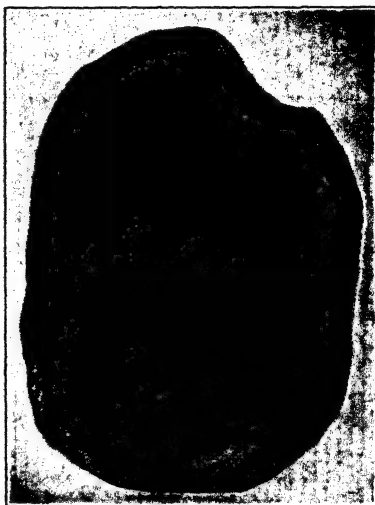


FIG. 339.—Embryoma. The homogeneous appearance of the cut surface is in striking contrast to the variegated surface of hypernephroma. The kidney is at the right of the tumor.



FIG. 340.—Wilms' tumor, showing a combined carcinomatous and sarcomatous appearance.  $\times 150$ .



readily explained by recalling that the epithelium of the urinary tract is derived from mesoderm (intermediate cell mass); the convoluted tubules develop from undifferentiated mesenchyma which has the appearance of cellular connective tissue in which glandular structures are formed. This is exactly the appearance presented by the usual form of Wilms' tumor. The occasional formation of muscle and cartilage is a perversion of growth on the part of the embryonic mesenchymal cells.

**OTHER TUMORS.**—*Fibroma* occurs fairly often as a small circumscribed nodule in a pyramid or papilla. Narrow tubules are usually scattered through the fibrous tissue. The lesion is rather a *hamartoma* than a true tumor, i.e., a developmental defect in tissue combination (*hamartia*, defect) with a limited capacity for aberrant growth. *Adenoma* forms a similar nodule in the cortex. It consists of tubules, sometimes lined by the same clear type of cell that is so characteristic of hypernephroma, and thus providing additional evidence for the tubular origin of that tumor. There may be cyst formation with papillary processes, such a tumor being really a *papillary cystadenoma*. *Lipoma* and *sarcoma* are rare tumors; most sarcomas develop from the capsule and invade the cortex secondarily. *Villous papilloma* of the pelvis is described in another section.

## CIRCULATORY DISTURBANCES OF THE KIDNEY

**CHRONIC VENOUS CONGESTION.**—The congestion is due to the ordinary causes, i.e., cardiac disease, and obstruction in the pulmonary circulation from emphysema, etc. The entire kidney is congested, but particularly the pyramids which are very dark. It is much firmer than normal, a condition known as *cyanotic induration*, and due partly to the increased blood content, partly to thickening of the capillary walls, but not to any increase in the interstitial tissue. The glomerular capillaries are greatly dilated and engorged with blood, and there may be red cells in the capsular space owing to rupture of the distended capillaries. In this condition, known clinically as *stasis kidney* and *cardiac kidney*, the urine may be diminished in amount, and may contain albumin and sometimes red blood cells. The dye excretion may fall low, but the concentrating power remains normal. Under treatment directed to the heart the condition of the urine may rapidly clear up.

**INFARCTION.**—The kidney is one of the commonest sites of infarcts. The cause of the vascular obstruction is usually arterial embolism, but it may be due to thrombosis of the small arteries. The infarct shows the usual characters which are described in Chapter 3. The necrotic area is surrounded by a zone of congestion, which in the earlier stages of the process may show much hemorrhage. For this reason there may be red cells in the urine at this stage. On the other hand, the urine is often normal. A renal infarct is usually without symptoms, there may be pain and tenderness over the kidney, and in exceptional cases the condition may simulate perforation of a viscus.

**SYMMETRICAL NECROSIS OF RENAL CORTEX.**—This fortunately rare and fatal condition is marked by anuria at the outset, and runs a clinical course similar to that produced by extirpation of both kidneys. It is twice as common in pregnancy (late stage) as in the non-pregnant state, occurring in both sexes and at any age. It is in essence a massive ischemic cortical infarction including the columns of Bertin. This massive lesion is the result of the coalescence of innumerable small infarcts. The gross picture is so characteristic that it can be recognized at a glance. Almost the entire cortex, with the exception of a very thin surface layer supplied by the capsular arteries, is a bright yellow outlined with red. A similar appearance is seen in the massive necrosis produced by the so-called elixir of sulphanilamide in which

the solvent was di-ethylene glycol. The lesion is an ischemic necrosis due to thrombosis of large numbers of small arteries and arterioles (Fig. 341). The walls of these vessels are necrotic. The primary lesion appears to be in the arterial wall, and it is probable that it is of the nature of an allergic reaction in this tissue<sup>8</sup> (Duff and More), a view which would explain the suddenness of onset. Similar small necrotic and arterial lesions are occasionally found in the adrenals, spleen and bowel. For further details regarding this remarkable condition the review by Duff and More should be consulted.

**ORTHOSTATIC ALBUMINURIA.**—What has been called benign albuminuria is of common occurrence in children and young adults, and is due, certainly in many cases, to a circulatory disturbance of the kidney. The distinguishing feature of the albuminuria is that it is absent when the person is lying down and appears when he assumes the erect posture. For this reason it is called orthostatic or postural albuminuria. The albumin is most marked in a specimen passed after the person has been up for some little time in the morning. It is commonly associated with marked lordosis of the lumbar spine (Jehle). When this lordosis is corrected, as by the child putting his foot on a stool, the albuminuria disappears even though the erect position is maintained. The vena cava lies to the right of the mid-line, so that the left renal vein has to cross the vertebral column, and is liable to be compressed if lordosis is at all marked. When catheters are placed in the ureters of a person who suffers from this condition, it will be found that when he assumes the erect (and lordotic) position the urine coming from the left ureter will contain albumin, while that coming from the right is normal (Sonnen). There may be anuria for one-half hour on the part of the ischemic left kidney, while the right kidney continues to secrete normal urine. The condition is an anomaly, but can hardly be called pathological. It tends to disappear as the person grows up and the lordosis lessens. The prognosis is excellent.

**HEMATURIA.**—This subject may be considered in connection with circulatory disturbances, although it is usually due to quite different causes. Blood in the urine may come from the urethra, bladder or kidney. Only the renal causes are considered here. In some cases the blood can be seen with the naked eye; in others it can only be seen with the microscope. In the latter group it is better to speak of red cells rather than blood in the urine. (1) The hematuria may be due to *circulatory disturbances*, e.g., chronic venous congestion, infarction. (2) *Inflammatory and necrotic conditions*, e.g., acute glomerulonephritis, embolic glomerulonephritis, focal nephritis, malignant nephrosclerosis. (3) *Tuberculosis* of the kidney. (4) *Tumors*. The common cause is hypernephroma, but papilloma or carcinoma of the renal pelvis may occasionally cause bleeding. (5) *Renal calculus*, the stone either remaining in the pelvis or passing down along the ureter. (6) *Essential hematuria* is a

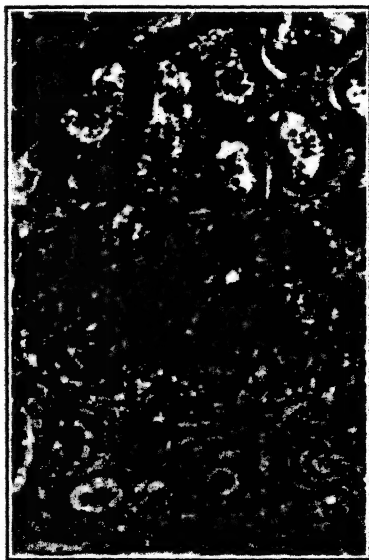


FIG. 341.—Symmetrical necrosis of renal cortex.

condition in which there is hemorrhage, sometimes severe, from one kidney, but when the condition is removed no cause is found. In most cases there is probably a focal nephritis which has been overlooked, or a varicosity in one of the renal papillæ.

### DEGENERATIONS OF THE KIDNEY

**TUBULAR DEGENERATION.**—This is not an entity but a convenient term to cover a diversity of conditions. *Cloudy swelling* is the commonest of all kidney lesions. It may occur in any febrile or infectious disease. Postmortem changes mimic it closely, and it is often difficult to know how much of the change is antemortem, how much postmortem, unless the material is very fresh. It has already been described in Chapter 2. All grades of severity of this albuminous degeneration may occur. The changes are most marked in the convoluted tubules. They may be classed as *nephroses*, but this is a dangerous term. It is safe enough when used in a strictly pathological sense, but it is apt to be seized by the clinician and perverted to his own uses. A large number of chemical poisons may be used experimentally to produce tubular degeneration or nephrosis, *viz.*, uranium nitrate, potassium bichromate, phosphorus, arsenic, and mercuric chloride. The last-named is the only one of clinical importance, for corrosive sublimate is often used for suicidal purposes (see page 569). In obstructive jaundice a well-marked bile nephrosis is common.

**FATTY DEGENERATION.**—Two forms may be recognized, the diffuse and the patchy. The *diffuse form* affects the entire parenchyma, especially the convoluted tubules. It is caused by pernicious and other anemias, diabetes, bacterial toxins, phosphorus, chloroform, etc. The condition is described in Chapter 3. The fat globules in the cells consist of neutral fat (glycerol esters). The *patchy form* is seen in the degenerated tubules of Bright's disease (glomerulonephritis, nephrosis, nephrosclerosis), and in amyloid degeneration. Owing to the irregular distribution the yellow fat gives the cortex a mottled or speckled appearance. Some of the fat is in the neutral form, but much of it is cholesterol ester. This lipid is present not only in the epithelial cells of the tubules but also in the interstitial tissue. Its nature can be recognized by the fact that it is anisotropic (doubly refractive) under crossed Nicol's prisms.

**VACUOLAR NEPHROPATHY.**—This indefinite term is a convenient description for the presence of clear well-defined vacuoles in the convoluted tubules, which may balloon out the cells and displace the nucleus to the base of the cell. They do not stain for either fat or glycogen, and may be presumed to be watery in character, a form of hydropic degeneration. Such vacuoles are seen after the intravenous administration of large quantities of glucose and particularly sucrose (Anderson). A striking degree of vacuolization has been observed in chronic intestinal disease, more especially ulcerative colitis (Kullna *et al.*). Here the condition may be related to deficiency in potassium or other electrolytes.

**AMYLOID DEGENERATION.**—The general pathology of amyloid disease is discussed in Chapter 3. It is a complication of a suppurative, tuberculous, or syphilitic lesion, but occasionally no evident cause can be found even at autopsy. The kidney is large and pale, and may closely resemble the "large white kidney" of subacute glomerulonephritis or nephrosis. But it is of firm consistence, and the cut surface has the characteristic translucent or waxy appearance of amyloid organs. When the iodine test is used the affected glomeruli stand out as dark-brown dots on the cut surface. If the progress of the disease is slow and the patient does not die of the original suppurative lesion, the kidneys may become contracted and granular.

*Microscopically* the amyloid is deposited in three situations: the glomeruli, the arterioles, and around the collecting tubules. It is a connective-tissue change, the epithelial changes being entirely secondary. The most striking lesions are in the glomeruli (Fig. 342). The deposit of amyloid occurs between the basement mem-

brane of the loop and the endothelium, so that the capillary loops are gradually closed. Some of the loops remain open for a long time, and through these damaged loops large quantities of albumin escape into the urine. In time the glomeruli are converted into large bloodless structureless masses of amyloid. When the glomerulus is occluded the corresponding tubule undergoes atrophy and is replaced by fibrous tissue. In this way marked tubular atrophy, fibrosis, and shrinking of the kidney may occur. In the earlier stages the tubules show marked evidence of degeneration, and the epithelium is filled with fatty and hyaline droplets and may contain cholesterol ester. Large homogeneous casts are formed in the tubules, and in the urine they are known as "colloid" casts. Much of the atrophy of the parenchyma is due not only to ischemia from glomerular atrophy but to pressure from the amyloid which gradually accumulates in the arteries and in the connective tissue around the tubules.

The *symptoms* are nephrotic in type, *i.e.*, massive albuminuria and edema, but if the patient lives long enough he may die of uremia with high non-protein nitrogen in the blood and hypertension. The nephrotic symptoms are based on hyperpermeable and still patent glomerular capillaries, whilst the terminal nephritic picture is that of the contracted ischemic kidney. Amyloid disease may last for many years. If the underlying cause can be arrested, as in syphilis, the amyloid disease may also cease to progress and even retrogress. Experimental evidence shows that amyloid material may become absorbed, and perhaps this may occur in man.

**DEPOSITS OF PIGMENT.**—*Blood pigment* may accumulate in the cells of the convoluted tubules when there is much blood destruction and the hemoglobin passes through the glomeruli and is concentrated in the tubules. This is well seen in pernicious anemia and paroxysmal hemoglobinuria. The granules of hemosiderin give the Prussian blue reaction for iron. Casts of hematin granules are seen in the tubules as the result of hemoglobinuria from unsuitable blood transfusion. *Bile pigment* may accumulate as fine granules in the cells of the convoluted tubules in persistent jaundice. In severe cases of jaundice of the new-born the pigment may be deposited in the apices of the pyramids, a condition known as *bilirubin infarcts*. A much commoner condition seen in new-born children is *uric acid infarcts*. They take the form of yellow streaks at the apices of the pyramids, and consist of deposits of urates in the collecting tubules. It is probable that they soon disappear. When melanin is excreted it appears in the cells of the loop of Henle.

*Glycogen deposits* occur in von Gierke's disease and also in severe cases of diabetes mellitus, although they are more rarely seen since the introduction of insulin. In diabetes the cells chiefly affected are those lining the loop of Henle. The affected cells are large and perfectly clear owing to the glycogen being dissolved out, so that



FIG. 342.—Amyloid disease of the kidney. The glomerulus is greatly enlarged by the amyloid, but the presence of blood cells (black) shows that the circulation is still going on.  $\times 275$ .

the tubule has a very striking and characteristic appearance. It is probable that the glycogen is derived from the sugar in the urine.

## ATROPHY AND HYPERTROPHY OF THE KIDNEY

*Atrophy* of the kidney may occur to a slight degree in general conditions of atrophy such as old age, but the only cause of real importance is loss of the blood supply. This may be caused by arteriosclerosis, which may affect the larger branches of the

renal artery (senile contracted kidney) or the arterioles (primary contracted kidney). Glomerular ischemia, the result of glomerulonephritis, leads to disappearance of the tubules and shrinking of the kidney (secondary contracted kidney). Sometimes one part of the kidney may be very atrophic, the remainder only partially so. There may be congenital hypoplasia. Pressure atrophy is typically seen in hydronephrosis, where the constant pressure of retained urine causes marked atrophy, first of medulla and later of cortex. The nephrons disappear and are replaced by fibrous tissue.

*Hypertrophy* of the kidney is compensatory. It is seen in its most extreme form when one kidney has been removed, is congenitally absent, or shows marked hypoplasia. In congenital absence of the kidney the weight of the surviving kidney may equal that of the two kidneys. There is no increase in the number of glomeruli and tubules, but they become larger. Between areas of arteriosclerotic atrophy the remaining portions may show a good deal of hypertrophy, which is most readily recognized in the convoluted tubules. The lining cells become larger, the lumen is dilated, and papillary growths may project into the lumen.

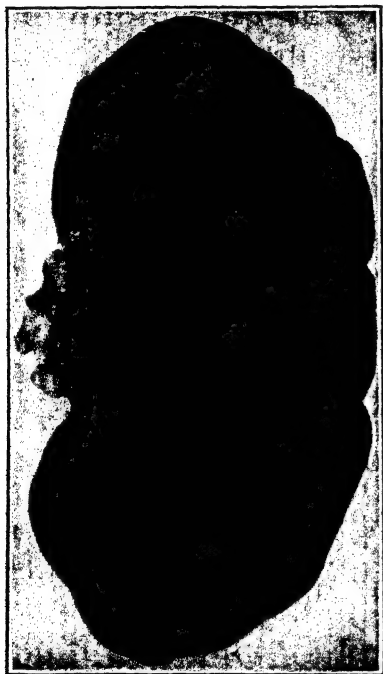


FIG. 343.—Fetal lobulation of the kidney.

## CONGENITAL ANOMALIES OF THE KIDNEY

*Fetal lobulation* is the most common anomaly. The furrows which separate the original lobules fail to disappear, so that the surface remains lobulated (Fig. 343). *Horse-shoe kidney* is also common. The kidneys are fused together, usually by their lower poles. The ureters pass down in front of the connecting bridge of tissue. *Agenesis* or absence of one kidney is usually associated with absence of the ureter. The other kidney is double the normal weight (compensatory hypertrophy). *Apasia* or marked *hypoplasia* is not very rare. The kidney may be a mere structureless rudiment, or may appear to be a normal small kidney. The other kidney is correspondingly large. *Dystopia* means displacement of the kidney, but the displacement is not active; the kidney has failed to migrate upward to its normal position, and remains in its primitive position, usually at the pelvic brim or the

bifurcation of the aorta. The ureter is naturally short, for it has never been of normal length, and as vascularization of the kidney does not occur until the final resting place is reached, the vessels will usually come off the lower end of the aorta. *Congenital cystic disease*, the most important of all the congenital anomalies of the kidney, has already been described.

## RENAL PELVIS, URETER, AND BLADDER

The pelvis of the kidney, the ureter, and the bladder are so closely related embryologically, functionally, and structurally that it is natural that the pathological conditions from which they suffer should be very similar. All are lined by stratified squamous epithelium, for the function of all three is either conduction or storage of urine, not secretion or absorption.

**Effect of Obstruction.**—Obstruction to the outflow of urine may cause dilatation of the bladder, ureter, or pelvis of the kidney (hydronephrosis), depending on the site of the obstruction. The obstruction may be in the urethra, bladder, or ureter. In the male urethra obstruction is due to *urethral stricture*, nearly always gonorrheal in origin. In the bladder the common cause is *enlargement of the prostate*, but a *tumor of the bladder* may obstruct the opening of one, sometimes both ureters, producing hydronephrosis. A *calculus* may block the renal pelvis, ureter, or urethral opening in the bladder. *Stricture of the ureter* may be due to scarring following injury caused by the passage of a calculus, or, as shown by Hunner, there may be local inflammation of the wall of the ureter due to hematogenous infection with the formation of one or more strictures (Hunner stricture of ureter). Stenosis of the lower end of the ureter for no apparent reason is probably congenital. *Movable kidney*, a condition in which the normal supports of the kidney are relaxed, allowing the organ to slip downward, may lead to kinking of the ureter and intermittent hydronephrosis. An *aberrant renal artery* passing across the ureter to the lower pole of the kidney may in exceptional cases cause sufficient pressure on the ureter to produce hydronephrosis. It is evident that if the obstruction is in the urethra or bladder the hydronephrosis will be bilateral, whereas if it is in the ureter or the ureteric opening in the bladder, the hydronephrosis will be unilateral.

Obstruction in the urethra (male) leads to dilatation and hypertrophy of the bladder. The proportion varies, just as it does in the gall-bladder and other hollow viscera when they are obstructed. The natural tendency is to dilatation, but there is a compensatory muscular hypertrophy, although this may be largely absent in old men. The hypertrophy leads to marked thickening of the wall of the bladder, and bands of muscle which normally have a reticulated arrangement under the mucosa become very prominent and stand out as trabeculae. The trabeculae are separated by depressions, and one or more of these may become enlarged so as to form a diverticulum. The dilatation of the urinary tract extends to the ureters and to the pelvis of the kidney. Infection is a common complication owing to the accumulation of stagnant urine, and the bladder, wall of the ureter and pelvis of the kidney show an inflammatory thickening in addition to

the dilatation. The real danger of obstruction is its effect on the kidney, and this will now be considered.

**HYDRONEPHROSIS.**—This is a dilatation of the renal pelvis and calyces with destruction of the kidney substance (Fig. 344). Hydronephrosis is caused by obstruction to the outflow of urine. The obstruction may be congenital or acquired.

*Congenital* obstruction takes the form of valve-like folds of the mucosa which are present in the fetus and sometimes at birth, or definite constrictions. These lesions, which are readily overlooked by the pathologist unless searched for with particular care, are commonest at the pelvi-

ureteric junction, but also occur at the pelvic brim and in the intravesical portion of the ureter. The most extreme examples of hydronephrosis belong to this group, because the condition is symptomless until it becomes far advanced.

*Acquired* obstruction may take the form of: (1) obstruction in the *urethra* from stricture and enlargement of the prostate; (2) obstruction in the *bladder* due to a calculus or to the internal sphincter being unable to open owing to neuromuscular dysfunction (tabes, injury to cord, etc.); (3) obstruction in the *ureter* due to a stone at the upper or lower end, stricture of the ureter, pressure of an aberrant branch of the renal artery, or kinking of the ureter. The most extreme forms of dilatation are caused by gradual partial obstruction, but sudden complete obstruction, as from ligation of the ureter, may lead to a moderate degree of dilatation followed by hydronephrotic atrophy. If renal ischemia is added to urinary obstruction, the destruction of tissue is much more rapid.

Experimental ligation of the posterior branch of the renal artery causes infarction of from one-third to one-half of the kidney; when this is combined with total ureteral obstruction enormous sacculations of the infarcted area are produced in a remarkably short time (Hinman and Hepler).

Some degree of dilatation of the ureter with hydronephrosis is common in pregnancy. This is not due, as used to be believed, merely to pressure on the ureters by the enlarged uterus. The main factor is the hormone complex of pregnancy, which causes not only relaxation of the smooth muscle of the uterus and gall-bladder, but also of the ureters. The effect is dependant on the presence of the placenta, and can be observed to develop in the monkey long after the fetus has been removed (van Wagenen and Jenkins). Mechanical pressure no doubt plays a secondary part.



FIG. 344.—Hydronephrosis. The renal pelvis and calyces are dilated. The ureter is blocked by a calculus.

The pelvis and calyces are dilated, sometimes to an enormous extent. The normal pelvis has an average capacity of 7 to 10 cc., but it may be distended so as to contain several liters. The pyramids are first destroyed by the dilatation of the calyces, and the cortex follows, until finally the kidney is converted into a thin-walled lobulated bag of watery fluid, the greatly distended calyces being separated by incomplete septa. Ischemia produced by pressure of the retained fluid is probably a large factor in the atrophy and destruction of the renal parenchyma. If infection is superadded the condition becomes an infected hydronephrosis. The wall of the sac will be thicker and the lining more rough as the result of infection.

*Microscopically* the first change is marked by atrophy of the tubules, while the glomeruli may appear fairly normal. This dissociation of lesions may be very striking, and is peculiar to hydronephrosis (Fig. 345). In course of time the glomeruli become fibrosed, and the renal parenchyma is replaced by fibrous tissue. Even in the advanced stages small areas can be found in which the glomeruli and tubules are apparently normal, and are probably continuing to secrete urine.

One of the problems of hydronephrosis is how it is that the contents of the hydronephrotic sac are fresh and clear instead of stagnant and stinking. Moreover, normal secreting tissue can be found even in cases of complete obstruction. It is evident that *absorption* of the fluid must occur, thus allowing a continual circulation. It has always been thought that this absorption must take place through the tubules, but Hinman and Lee-Brown have shown that absorption in hydronephrosis takes place from the pelvis directly into the veins. This *pyelovenous backflow*, as Hinman calls it, occurs from the minor calyces into the straight veins at the base of the pyramids. By using this mechanism the entire venous system of the kidney can be injected through the hydronephrotic pelvis.

**Inflammation.**—Infection of the pelvi-vesical tract may occur from the urethra, kidney, or neighboring organs. The short female urethra accounts for the frequency of lower urinary tract infection in women and children. In the male, infection from below is due to retention (stricture of urethra, enlarged prostate), or the passage of an infected catheter. Infection of the bladder usually comes from the kidney, unless there is some predisposing

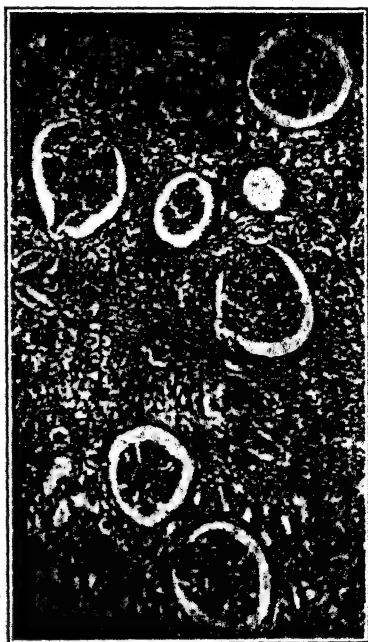


FIG. 345.—Hydronephrosis, showing disappearance of tubules.  $\times 65$ .



cause in the bladder such as retention or stone. The healthy bladder is remarkably resistant to infection, and when pyogenic bacteria are introduced into its cavity they rapidly disappear. Occasionally infection may come from a neighboring organ, as in inflammation of the appendix or the female pelvic organs. The common infecting organism is *Bacillus coli*, with an acid urine. The pyogenic cocci are next in frequency, and they turn the urine alkaline owing to the production of ammonia. Two of the most troublesome organisms are *Bacillus proteus* and *Bacillus pyocyaneus*, because, being Gram-negative, they are resistant to penicillin. Fortunately they respond to streptomycin.

Inflammation of the bladder is called *cystitis*, while inflammation of the renal pelvis is *pyelitis*. The inflammation may commence in the pelvis and infect the bladder, or begin in the bladder and pass to the kidney, there causing a pyelonephritis.

*Cystitis* may be acute or chronic. In the *acute form*, which is likely to be due to the pyogenic cocci, the mucous membrane is swollen, red, and hemorrhagic. Small ulcers develop, the surface is covered with shreds of epithelium, and small clear cysts are formed on the trigone. Microscopically there is congestion of the submucosa and infiltration with inflammatory cells, the superficial layers of mucosa may be desquamated, but the main substance of the wall is intact. In *chronic cystitis* the appearance depends on the presence or absence of obstruction. When there is no obstruction the wall is thickened owing to the formation of inflammatory tissue; the size of the cavity becomes smaller instead of larger. When there is obstruction as well as inflammation, the bladder is dilated and the wall may be either thickened or atrophied. Polypoid masses of hypertrophied mucous membrane may project into the cavity. The trabeculation, pouching, and formation of diverticula have already been described. Microscopically the mucosa shows patchy ulceration, with areas of granulation tissue formation corresponding to the polypoid masses, the submucosa is fibrosed and infiltrated with chronic inflammatory cells, and the fibers of the muscular coat are separated by an abundant formation of connective tissue.

**PYELITIS CYSTICA.**—Occasionally numerous tiny cysts may be observed in the renal pelvis, a condition known as pyelitis cystica. Similar lesions occur in the ureter (ureteritis cystica) and bladder (cystitis cystica). As the result of chronic inflammation the epithelium grows down to form small nests of cells. These cells are then arranged to form glands, which develop into cysts.

**HUNNER'S ULCER.**—This condition is also known as *interstitial cystitis*, "elusive" ulcer owing to the fact that both symptoms and ulcer may come and go, and by still other names. The cause and nature of the disease are unknown. The affected area shows marked inflammatory thickening, and in the center there is a minute exquisitely tender ulcer, often little more than an erosion. The microscopic changes are those of chronic inflammation. The most important sign of this crippling and chronic condition is bleeding from the lesion seen with the cystoscope when the bladder is distended. The urine contains neither pus nor bacteria.

*Leukoplakia* is a rather rare accompaniment of chronic inflammation. It may be confined to the renal pelvis or bladder, or it may involve pelvis, ureter and bladder. The mucosa is pale and wrinkled so as to resemble skin, and the change is usually patchy with rather clean-cut areas. It is an epidermoid change, a metaplasia of the transitional type of epithelium to a squamous stratified type. Both in the renal

pelvis and in the calyces it may be a precursor of the non-papillary type of carcinoma, so that it may be regarded as a precancerous condition.

**Tuberculosis.**—Tuberculosis of the *renal pelvis* occurs at an early stage of tuberculosis of the kidney, for the initial lesion in the pyramid soon spreads to one of the calyces. In the *ureter* the infection spreads in the submucosa, with ulceration of the overlying mucous membrane and eventual cicatrization. The entire wall is rigid and fibrosed, and the ureter may remain wider than normal instead of being stenosed. The chief lesions are usually in the upper or the lower third.

In the *bladder* the infection is usually secondary to renal tuberculosis, but it may come from the prostate, seminal vesicles, and epididymis, and in rare cases from adjacent pelvic organs, *e.g.*, Fallopian tubes. In renal cases the disease begins at the ureteric opening, in prostatic cases it begins at the neck of the bladder. In the common renal cases an area of hyperemia and swelling is first seen around the opening of the ureter, followed by the appearance of tubercles and vesicles. The opening of the ureter may project like a crater into the bladder. The tubercles are formed in the subepithelial tissue, and the overlying epithelium becomes ulcerated. The tuberculous ulcer has a round outline, ragged, overhanging edges, and a gray, shaggy floor. Most of the symptoms of renal tuberculosis are due to bladder irritability. If the kidney is removed and the continued reinfection of the bladder stopped, the vesical lesions may heal completely if the disease has not gone too far. The urine is acid, but septic infection may be superadded, when the reaction will become alkaline.

**PARASITES.**—Infection with *Bilharzia hæmatobia* (*Schistosoma hæmatobium*) is very common in some tropical countries, particularly in Egypt. The characters of the parasite are described in Chapter 8. The ova pass in large numbers from the vesical veins, where they are laid by the female, into the subepithelial connective tissue of the bladder. Here their sharp spines excite great irritation, as a result of which granulation tissue is formed which causes great thickening of the mucosa, as well as papillary vascular projections, from which bleeding readily occurs when the bladder contracts. Hematuria is therefore a constant symptom, and the ova are readily recognized in the urine. Carcinoma is a fairly common development, and must be related causally to the parasitic infection. Bilharzial lesions may occur in the ureter and renal pelvis. *Eustrongylus gigas*, a round worm, is a fairly common parasite in the renal pelvis of animals, and in rare cases has been found in man.

**Calculus.**—A urinary calculus may be formed in the renal pelvis of the bladder. It may cause symptoms in the kidney, ureter, or bladder. It consists of a nucleus of organic material around which urinary salts are deposited in concentric layers, which are bound together by a colloid matrix of organic matter. The salts, although crystalline in the urine, are in the form of amorphous granules in the calculus. Urinary calculi may consist of: (1) uric acid and urates, (2) calcium oxalate, and (3) calcium and ammonio-magnesium phosphate. These constituents are often combined. As regards frequency the calculi are oxalate in about 60 per cent of the cases, phosphate in 30 per cent, uric acid in 4 per cent, urate in 4 per cent, and cystine in 2 per cent. The center of the stone may consist of uric acid or oxalate, with on the outside phosphates the result of infection and decomposition of the urine.

The *uric acid stone* is of moderate hardness, brown in color, and shows concentric rings on the cut surface. The uric acid is usually combined with urates and sometimes with oxalates. It occurs in acid urine. The *oxalate stone* is the commonest form of calculus and consists of calcium oxalate. It is extremely hard, and the surface is rough or may be spiny (mulberry calculus). On this account it produces marked irritation, and is often dark because of staining with blood. The cut surface shows concentric laminæ, but not so clearly defined as in the uric acid variety. The outer layers often contain urates. The *phosphatic stone* consists of calcium phosphate and triple phosphates (ammonio-magnesium phosphate). It is quite different from the others, for it is white, smooth, chalky, and easily broken up. It occurs in alkaline urine. Deposits of phosphates are often formed on the surface of uric acid and oxalate stones owing to a change in the reaction of the urine, the result of infection. The uric acid and oxalate stones occur apart from gross infection in the renal pelvis and sometimes in the bladder, and are known as *primary stones*. The phosphatic stone is formed as the result of infection usually in the bladder but sometimes in the renal pelvis, and is therefore called a *secondary stone*.

*Etiology.*—The etiology of urinary calculi is by no means clear, but four possible factors may be considered: (1) infection, (2) high concentration of urinary salts, (3) vitamin A deficiency, (4) parathyroid tumor. *Infection* is all-important in the secondary phosphatic stone which is a common consequence of the cystitis associated with enlargement of the prostate. It is probable that a mild infection is the starting-point of most if not all the uric acid and oxalate stones in the kidney, although it is not readily detected like the gross infection which is responsible for the secondary phosphatic stone. Ordinary pyelitis (pyelonephritis) is seldom associated with stone formation. It is much commoner in women, whereas renal calculus is commoner in men. The type of stone depends much on the reaction of the urine, and that depends on infection. A uric acid or oxalate stone is formed when the urine is acid. Infection with pyogenic cocci turns the urine alkaline, and the stone becomes coated with phosphates. Subsequent infection with the colon bacillus may bring back an acid reaction, with the deposition of uric acid or calcium oxalate. In this way a stone may contain all three principal constituents.

The *concentration of crystalline salts* is a second factor, although the urine may be loaded with various crystals for long periods without the formation of a stone. The relation of the colloids of the urine to the crystalloids is probably of great importance, and this in turn is dependent on infection. The presence of an abnormal colloid or the absence of a normal one may cause the crystalloids to be precipitated, especially if they are present in excess. *Parathyroid tumor* is a possibility which must be considered in every case of renal calculus, especially if bilateral and recurring. As a result of the hyperparathyroidism calcium is removed from the bones, the blood is flooded with calcium, and this tends to be deposited in the renal pelvis. Such stones will contain a high proportion of calcium and phosphorus. A serum calcium above 11.5 and phosphorus below 3.5 in a case of renal calculus should suggest the possibility of parathyroid tumor. *Vitamin A deficiency* is a cause of renal calculi in the experimental animal.

Lack of this vitamin leads to keratinization and desquamation of the epithelium of the renal pelvis which may form the nidus for a stone. It also affects the urinary colloids, so that they fail to hold the crystalloids in solution.

Randall points out that a small "milk patch," usually not more than 2 mm. in diameter, may sometimes be seen on a papilla. This corresponds with a deposit of calcium in the cells lining the tubules. The epithelial covering becomes lost, and a tiny black dot is seen on the milk patch. On this basis a secondary crystalline deposit, the true stone, is formed, which tends to undermine the patch so that the latter is finally torn away. It seems probable that at least some renal stones may originate as a so-called Randall plaque. Anderson has shown that microscopic calculi can be demonstrated in the papillæ of every kidney which is examined sufficiently carefully. The fact that large or symptomatic kidney stones are so uncommon indicates that some still unknown metabolic or other systemic factor is necessary for the deposition of large quantities of urinary salts on the nidus.

The *geographical distribution* of stone is striking, and probably related in part to vitamin deficiency. In Egypt and in some parts of India it is common, but in North America it is comparatively rare. In eastern countries urinary stones are commonest in children, while in Europe and North America they occur in the later years of life and are seldom seen in children. A hundred years ago stone formation was common among European children. The change is probably due to the great improvement in the diet of the modern child.



FIG. 346.—Large coralline calculus in renal pelvis extending into the calyces.

**STONE IN THE KIDNEY.**—A renal calculus is formed in the pelvis. It is usually uric acid or oxalate in type, and is much commoner in men than in women. It may be single or multiple, and may remain in the kidney or pass down into the bladder. During its passage along the ureter it excites violent spasmodic contractions which are responsible for the pain of renal colic. The large stone is unable to enter the ureter and is therefore often a silent stone. "It is the little stones, like little dogs, that are likely to make the most noise" (Cabot).

The chief *effects* on the kidney are retention, infection, and ulceration. If the stone blocks the opening of the ureter *hydronephrosis* will result. The stone may increase in size, and sometimes has a branched appearance owing to extensions into the dilated calyces; this type is known as a coralline calculus (Fig. 346). If the stone is impacted in the ureter so as to cause complete obstruction, there may be anuria and atrophy of the kidney. Infection is a common accompaniment of calculus, and by altering the reaction of the urine it may alter the external composition of the stone. If dilatation of the pelvis has not occurred, the infection will cause *pyelo-*

*nephritis*. If dilatation has occurred there will be *pyonephrosis*. Pressure of the stone on the kidney causes *ulceration*. Much of the kidney may be destroyed in this way even without much infection. The stone has been known to ulcerate through the wall of the pelvis and pass into the abdominal cavity.

**STONE IN THE URETER.**—The calculus may be arrested in the ureter as it passes downward. This usually occurs at the upper end or at the lower end where the ureter is constricted in its oblique passage through the bladder wall. The pressure of the stone causes ulceration of the wall. The ureter above the obstruction becomes dilated, and impaction of a ureteral calculus is the cause of some of the most extreme forms of hydronephrosis.

**STONE IN THE BLADDER.**—A vesical calculus may form in the bladder, or it may originate in the renal pelvis, pass down into the bladder, and there grow greatly in size. There may be one or many stones. The stone which begins in the bladder usually consists of phosphates, and forms in the alkaline infected urine which is retained in enlargement of the prostate and stricture of the urethra. A stone which has reached the bladder from the kidney is usually a uric acid stone, but may be an oxalate stone. In the bladder it gives rise to infection, so that phosphates are deposited on the surface, and the cut surface shows a white outer zone of phosphate and a laminated dark nucleus of uric acid or oxalate. A vesical calculus may reach a very great size. The *effect on the bladder* is the same as in the renal pelvis, *i.e.*, there may be retention due to obstruction of the urethral opening, infection, and ulceration from pressure. The most characteristic symptom is hematuria, owing to irritation of the mucosa each time the bladder contracts. On the other hand, it is remarkable how silent a large smooth phosphatic stone may be. The irritation of the stone does not predispose to tumor formation.

**Tumors.**—Tumors of the renal pelvis, ureter and bladder are of the same type, for all are lined by the same transitional epithelium. The bladder tumors are much the most common, and they will be described as the type. They may be divided into three groups: (1) papilloma, (2) papillary carcinoma, and (3) non-papillary carcinoma. In a study of 280 cases Aschner found 90 papillomas, 137 papillary carcinomas, and 43 non-papillary carcinomas. It is often very difficult to decide if a biopsy specimen should be placed in the first or second group, and the coagulation produced by the transurethral punch used to remove the tissue makes the differentiation still more difficult. A benign papilloma has a strong tendency to become carcinomatous. For these reasons it is best to regard all epithelial tumors of the bladder as potentially malignant.

Workers in aniline dye factories are prone to develop the disease, the lung being the chief route of absorption. The carcinogenic substance in the dye is now known to be beta-naphthylamine. Dogs fed or injected with beta-naphthylamine develop tumors of the bladder but not of the kidney (Hueper, *et al.*). It is of interest to note that the injection of beta-anthraquinoline produces kidney tumors but not bladder tumors (Sempson and Morelli). There is no relation between carcinoma of the bladder and vesical calculus. The sharp-spined ova of *Bilharzia hematobia* seem

to act as a carcinogen in the bladder wall. The highest incidence of cancer of the bladder is in Egypt, where schistosomiasis is extremely prevalent.

The *villous papilloma*, which by some is regarded as a Grade 1 carcinoma, is a delicate many-fingered growth which springs from a small area of mucosa and unfolds its fragile processes when the bladder is filled with water, until it looks like a piece of seaweed floating in a marine pool when viewed with the cystoscope. In other cases the pedicle is broad and the processes more squat, so that the tumor has a raspberry appearance, whether from diffusion of the irritant or from the implantation of the growths it is hard to say. There is said to be a strong tendency to implantation of tumor cells, as the surgeon may discover after he has "successfully" removed the tumor, but it is more probable that the growth of subsequent tumors is evidence of multicentric origin rather than that implantation of tumor fragments has occurred on so smooth a surface. The usual sites are: (1) just external to the openings of the ureters, (2) at the neck of the bladder, and (3) in the vault. The villi consist of a very delicate framework of connective tissue containing large capillary loops and covered by transitional epithelium (Fig. 347). It is easy to understand how easily these fragile processes are injured when the bladder contracts, so that hemorrhage from the capillary loops is the essential symptom.

The *papillary carcinoma* is the commonest form. It usually arises from a benign papilloma, the change occurring in any part of the tumor. The tumor may be infiltrating or non-infiltrating. It is the latter which may resemble so closely the benign papilloma. Indications of malignancy are a departure from the normal histology (loss of palisade arrangement), variations in the size, shape, and staining characters of the cells, hyperchromatic nuclei, and the presence of numerous mitotic figures.

The *non-papillary carcinoma* is the least common form. The tumor extends under the mucosa and infiltrates the wall deeply. There is necrosis and ulceration, so that the tumor may take the form of a carcinomatous ulcer. Microscopically it may be scirrhous or medullary in type. An epidermoid carcinoma may develop on top of a leukoplakia. The rarest epithelial tumor is an *adenocarcinoma* developing from glands occasionally present in the trigone of the bladder.



FIG. 347.—Papilloma of bladder. The thin-walled vessel can be seen in the middle of the villus.  $\times 100$ .

Involvement of the opening of the ureter on each side leads to urinary retention and hydronephrosis, and as infection is easily added there is likely to be cystitis and pyonephrosis. Death may be due to uremia.

**SPREAD.**—Spread occurs to the iliac and lumbar glands. The lungs and liver may be infected through the blood late in the disease. There may be secondary growths in the bones. The low-grade form (papilloma) remains confined to the bladder.

*Tumors of the renal pelvis* are of the same type as those which occur in the bladder. So are the rare *tumors of the ureter*. The tumor is usually a malignant papilloma, and the wall of the pelvis may be covered with finely branched villous processes. These are friable and vascular, so that hemorrhage readily occurs. The tumor may block the ureter and cause hydronephrosis. There may be multiple tumors of the renal pelvis and bladder. A patch of leukoplakia, sometimes due to the irritation of a calculus, may be the starting point of an epidermoid carcinoma.

*Sarcoma* of the bladder is very rare. It is never papillomatous. *Myxoma* and *leiomyoma* are very rare; the myxoma occurs especially in children. A *dermoid cyst* may occur in the wall, giving rise to the passage of hair in the urine (pilimiction).

**MALAKOPLAKIA.**—This very rare condition is characterized by yellow, soft (*malakos*, soft), discrete nodules in the bladder mucosa. In addition to ordinary inflammatory changes the lesions present highly characteristic multinucleated giant cells containing calcified cytoplasmic inclusions known as Michaelis-Gutmann bodies. The condition is associated with cystitis.

**DIVERTICULUM.**—A diverticulum of the bladder is an uncommon condition. In chronic cystitis a certain amount of pouching may occur between the trabeculae of the wall. In the more marked cases it is probable that there is a congenital basis. The diverticulum may be very large, sometimes as large as the bladder itself. The wall may consist of muscle or only of mucous membrane. Carcinoma may develop inside the diverticulum.

**BONE FORMATION.**—The epithelium of the urinary tract (renal pelvis, ureter and bladder) has a curious osteogenic power. Experimental injury to the renal pelvis is followed by bone formation in the fibrous tissue external to the mucosa. Experimental implantation of bladder mucosa into the abdominal wall leads to bone formation (Huggins). The same result has been observed in rare cases in man after operations on the bladder, *e.g.*, prostatectomy.

## THE URETHRA

### GONORRHEAL URETHRITIS

This is a very acute suppurative condition. By the end of the second day the crypts in the wall of the anterior urethra are filled with pus cells containing gonococci, and by the third day the mucosa is extensively infiltrated, for the columnar epithelium offers no resistance. An acute inflammatory exudate is formed in the mucosa, and an abundance of pus is poured from the surface. The infection spreads in the submucosa until the posterior urethra (membranous and prostatic parts) is involved. Here the infection may linger for a long time in the glands which open on to the surface. The acute inflammation may subside in the course of a few weeks, the desquamated epithelium being replaced by epithelium of squamous type. In other cases the infection becomes chronic, being fed from foci in the posterior urethra. The mucous and submucous coats are converted into gran-



ulation tissue, which later becomes fibrosed and scarred. The scar tissue may contract, producing a stricture of the urethra.

*Stricture* usually develops in the bulbous urethra. The narrowing may be extreme, producing the results of obstruction which have already been considered (hydronephrosis, etc.). As there is no residual urine there is less chance of infection than in enlargement of the prostate, but if a catheter has to be used frequently the danger becomes great. When infection does occur, the patient may die of sepsis or of uremia.

Stricture may be due to trauma, or may be congenital (see below).

*Calculus* of the urethra is rare. It is the result of a stone from the kidney or bladder being stopped in the urethra.

**REITER'S SYNDROME.**—In 1916 Reiter described what is now recognized as a characteristic triad of symptoms, namely, urethritis, conjunctivitis and multiple arthritis, preceded by mild diarrhea. Reiter had only a single case, a young German officer, surely a remarkable example of an eponym being awarded as the result of a solitary observation. And yet nothing of consequence has been added to our knowledge of the condition in the intervening years. The etiology is unknown, although suspicion attaches to a pleuropneumonia-like organism. The disease is confined to young males. Biopsy in a few cases has shown a mild synovitis. The disease is self-limited and the prognosis excellent. It seems probable that the urethritis represents the primary lesion, and that the widespread arthritis and occasional skin rashes are allergic in nature. A full review of the literature will be found in Vallee's paper.

## CONGENITAL ANOMALIES OF THE LOWER URINARY TRACT

*Double ureter* is a condition in which the entire ureter or only the upper part is duplicated. There is a double pelvis, one in the upper part of the kidney, the other in the lower. If the doubling affects the entire ureter, there are two separate openings into the bladder. *Congenital dilatation of the ureters* may be due to a variety of causes. Bilateral dilatation in male children is likely to be caused by a congenital valvular obstruction in the posterior urethra from a persistent urogenital membrane or an exaggeration of the normal mucosal folds of the urethra. Unilateral dilatation may be due to congenital stricture of the ureter at its point of entrance into the bladder wall. The rare condition of *ureterocele* or cystic dilatation of that part of the ureter which lies within the bladder wall is due to congenital narrowing at the mucosal orifice; this gives rise to a characteristic bulging of the bladder wall at that point, which can be readily recognized with the cystoscope. Occasionally no obstruction of any kind can be found to account for the dilatation of the ureter; such cases are attributed to a hypothetical weakness of the neuromuscular mechanism of the wall of the ureter. *Ectopia vesicae* or *extroversion* of the bladder is a rare condition in which, owing to a congenital deficiency of the anterior wall of the bladder with an associated splitting of the anterior abdominal wall in the middle line, the interior of the bladder is exposed and the posterior wall may be extruded. The epithelium of the exposed mucosa undergoes metaplasia into an epidermoid type. The condition is often associated in the male with *epispadias*, the urethra remaining open on its dorsal aspect; in the female the clitoris may be split. *Patent urachus* is a rare condition in which urine may pass from the bladder to the umbilicus along the original line of the allantoids. Only part may remain patent, e.g., the outer or inner ends or the central portion. In the latter variety a cyst of the urachus may result.



## ADDITIONAL READING

- Acute Interstitial Nephritis.** KIMMELSTIEL: *Am. J. Path.*, 1938, 14, 737.
- Amyloid Kidney.** BELL: *Am. J. Path.*, 1933, 9, 185.
- Anemia in Nephritis.** CALLEN AND LIMARZI: *Am. J. Clin. Path.*, 1950, 20, 3.
- Aniline Tumors of Bladder.** HUEPER: *Arch. Path.*, 1938, 25, 856.
- Bilateral Cortical Necrosis.** ASH: *Am. J. Med. Sci.*, 1933, 185, 71. DUFF AND MORE: *Am. J. Med. Sci.*, 1941, 201, 428.
- Bright's Disease.** ADDIS AND OLIVER: *The Renal Lesion in Bright's Disease*, New York, 1931. ELLIS: *Lancet*, 1942, 1, 72. FAHR: In Henke-Lubarsch: *Handb. d. spez. path. Anat. u. Histol.*, 6, pt. 1, Berlin, 1925. OLIVER: *Architecture of the Kidney in Chronic Bright's Disease*, New York, 1939. RUSSELL: *Gt. Brit. Med. Res. Council, Spec. Rep. Series*, No. 142, London, 1929. VOLHARD AND FAHR: *Die Brightsche Nierenkrankheit*, Berlin, 1914.
- Crush Nephritis.** BYWATERS AND DIBLE: *J. Path. and Bact.*, 1942, 54, 111.
- Eclampsia.** DEXTER, WEISS AND OTHERS: *Preëclamptic and Eclamptic Toxemia of Pregnancy*, Boston, 1941.
- Experimental Glomerulonephritis.** MORE AND WAUGH: *J. Exp. Med.*, 1949, 89, 541.
- Experimental Renal Hypertension.** MUIRHEAD, *et al.*: *Arch. Path.*, 1949, 48, 234.
- Focal Glomerulitis.** GROSS AND MORNINGSTAR: *Am. J. Path.*, 1943, 19, 333.
- General References.** ALLEN: *The Kidney; Medical and Surgical Diseases*, New York, 1951. BELL: *Renal Diseases*, Philadelphia, 1950. McMANUS: *Medical Diseases of the Kidney*, Philadelphia, 1950.
- Glomerulonephritis.** BELL: *Am. J. Path.*, 1938, 14, 691. CAVELTI AND CAVELTI: *Arch. Path.*, 1945, 39, 148; 1945, 40, 158, 163. DUNN: *J. Path. and Bact.*, 1940, 51, 169. JONES: *Am. J. Path.*, 1951, 27, 991; 1953, 29, 33. McLEAN, *et al.*: *Arch. Path.*, 1951, 51, 1. MCGREGOR: *Am. J. Path.*, 1929, 5, 559. RINEHART: *Am. J. Path.*, 1953, 29, 21.
- Hydronephrosis.** HINMAN AND HEPLER: *Arch. Surg.*, 1925, 11, 578 and 649. HINMAN AND LEE-BROWN: *J. A. M. A.*, 1924, 82, 607. VAN WAGENEN AND JENKINS: *J. Urol.*, 1939, 42, 1010. WHITE: *Brit. J. Surg.*, 1925, 13, 247.
- Hypernephroma.** CREEVY: *Arch. Int. Med.*, 1935, 55, 895. LEARY: *Arch. Path.*, 1950, 50, 151. SMYTH: *Brit. J. Surg.*, 1939, 27, 266.
- Incompatible Blood Transfusion.** DE NAVASQUEZ: *J. Path. and Bact.*, 1940, 51, 413.
- Interacapillary Glomerulosclerosis.** ALLEN: *Arch. Path.*, 1941, 32, 33. BARRIE, *et al.*: *Can. Med. Ass. J.*, 1952, 66, 428. GOODOF: *Ann. Int. Med.*, 1945, 22, 373. HALL: *J. Path. and Bact.*, 1952, 64, 103. HARTROFT: *Am. J. Path.*, 1953, 29, 576. KIMMELSTIEL AND WILSON: *Am. J. Path.*, 1936, 12, 83. LAIPPLY, *et al.*: *Arch. Int. Med.*, 1944, 74, 354. SIEGAL AND ALLEN: *Am. J. Med. Sci.*, 1941, 201, 516.
- Interstitial Tissue of Glomerulus.** JONES: *Am. J. Path.*, 1951, 27, 991. MACCALLUM: *Bull. Johns Hopkins Hospital*, 1934, 55, 416.
- Juxtaglomerular Apparatus.** DUNIHUE AND CANDON: *Arch. Path.*, 1940, 29, 777. GOORMAGHTIGH: *Am. J. Path.*, 1940, 16, 409. McMANUS: *Lancet*, 1942, 2, 394. OBERLING: *Am. J. Path.*, 1944, 20, 155.
- Kidney in Bacterial Endocarditis.** BELL: *Am. J. Path.*, 1932, 8, 639. CHRISTIAN: *J. Mt. Sinai Hosp.*, 1942, 8, 427.
- Lower Nephron Nephrosis.** LUCKÉ: *Mil. Surgeon*, 1946, 99, 371. MALLORY: *Am. J. Clin. Path.*, 1947, 17, 427.
- Malakoplakia.** MORISON: *J. Path. and Bact.*, 1944, 56, 67.
- Nephrosclerosis.** BELL AND CLAWSON: *Arch. Path.*, 1928, 5, 939. GASKELL: *J. Path. and Bact.*, 1912, 16, 287. KIMMELSTIEL AND WILSON: *Am. J. Path.*, 1936, 12, 45. KLEMPERER AND OTANI: *Arch. Path.*, 1931, 11, 60. MCGREGOR: *Am. J. Path.*, 1930, 6, 347. SCHURMANN AND MACMAHON: *Virchows Arch. f. path. Anat.*, 1933, 291, 47.
- Nephrosis.** BELL: *Am. J. Path.*, 1929, 5, 587. CUBITT: *Brit. J. Surg.*, 1936, 24, 215. DIBLE IN HADFIELD: *Recent Advances in Pathology*, London, 1953. DUNN: *J. Path. and Bact.*, 1934, 39, 1; 1940, 51, 169. KIMMELSTIEL: *South. Med. J.*, 1953, 46, 175. McNEE: *J. Path. and Bact.*, 1922, 25, 425. MUNK: *Virchows Arch. f. path. Anat.*, 1908, 194, 527.
- Nephrotoxic Nephritis.** MASUGI: *Beitr. z. path. Anat. u. z. allg. Path.*, 1933, 91, 82; 1934, 92, 429. SMADEL AND FARR: *Am. J. Path.*, 1939, 15, 199.

- Papillitis Necroticans.** EDMONDSON, *et al.*: Arch. Int. Med., 1947, 79, 148. KNUTSEN, *et al.*: Am. J. Clin. Path., 1952, 22, 327. MUIRHEAD, *et al.*: J. A. M. A., 1950, 142, 627. ROBBINS AND ANGRIST: Ann. Int. Med., 1949, 31, 773. ROBBINS, *et al.*: New England J. Med., 1946, 235, 885.
- Perinephritic Abscess.** CAMPBELL: Surg., Gynec. and Obst., 1930, 51, 676.
- Polycystic Kidney.** BELL: Am. J. Path., 1935, 11, 373. KAMPMEIER: Surg., Gynec. and Obst., 1923, 36, 208. RITTER AND BAEHR: J. Urol., 1929, 21, 583.
- Pyelonephritis.** BELL: Surgery, 1942, 11, 261. FAHR: Virchows Arch. f. path. Anat., 1938, 301, 140. (Excellent review.) LONGCOPE AND WINKENWERDER: Bull. Johns Hopkins Hosp., 1933, 53, 255. MALLORY, *et al.*: Arch. Path., 1940, 30, 330. WEISS AND PARKER: Medicine, 1939, 18, 221.
- Reiter's Syndrome.** VALLEE: Arch. Int. Med., 1946, 77, 295.
- Relation of Kidney to Hypertension.** BELL AND CLAWSON: Arch. Path., 1928, 5, 939. BLALOCK: Physiol. Rev., 1940, 20, 159. FRIEDMAN AND KAPLAN: J. Exper. Med., 1943, 77, 65. GROLLMAN, *et al.*: Arch. Int. Med., 1951, 87, 379. GOLDBLATT: The Renal Origin of Hypertension, Springfield, Ill., 1948. MACKAY, *et al.*: Canad. Med. Assn. J., 1944, 50, 328. MORITZ AND OLDT: Am. J. Path., 1937, 13, 679. MUIRHEAD, TURNER AND GROLLMAN: Arch. Path., 1951, 51, 575. WILSON AND BYROM: Quart. J. Med., 1941, 10, 65.
- Renal Anoxia.** BADENOCH AND DARMADY: J. Path. and Bact., 1947, 59, 79. DARMADY, *et al.*: Lancet, 1944, 2, 809. MAEGRAITH, *et al.*: Lancet, 1945, 2, 293. MOON: Brit. Med. J., 1944, 1, 773. TRUETA, *et al.*: Lancet, 1946, 2, 237.
- Renal Infantilism.** PARSONS: Arch. Dis. Child., 1927, 2, 1. PRICE AND DAVIE: Brit. J. Surg., 1937, 24, 548.
- Renal Infarction.** ASCHNER: Am. J. Med. Sci., 1922, 164, 386. BARNEY AND MINTZ: J. A. M. A., 1933, 100, 1.
- Renal Lesions of Pregnancy.** BAIRD AND DUNN: J. Path. and Bact., 1933, 37, 291. WEISS, *et al.*: Trans. Assn. Am. Physicians, 1940, 55, 282.
- Renal Tuberculosis.** HARRIS: Brit. J. Surg., 1929, 16, 464. MEDLAR: Am. J. Path., 1926, 2, 401.
- Solitary Cysts.** HEPLER: Surg., Gynec. and Obst., 1930, 50, 668.
- Sulphonamide Nephritis.** BLACK-SCHAFER: Arch. Path., 1945, 39, 301. HARTROFT: Canad. Med. Assn. J., 1944, 51, 23. MERKEL AND CRAWFORD: J. A. M. A., 1942, 119, 770. RICH: Bull. Johns Hopkins Hosp., 1942, 71, 123, 375. SIMON: Am. J. Med. Sci., 1943, 205, 439. SOBIN, *et al.*: Am. J. Path., 1943, 19, 211.
- Toxemia of Pregnancy.** BELL: Am. J. Path., 1932, 8, 1.
- Tuberculosis of the Kidney.** BAND: Edinburgh Med. J., 1935, 42, 162.
- Tumors of the Bladder.** ASCHNER: Surg., Gynec. and Obst., 1931, 52, 979. KRET-SCHMER, *et al.*: J. Urol., 1934, 31, 423.
- Tumors of the Kidney.** FITE: Arch. Path., 1945, 39, 37. GESCHICKTER AND WIDENHORN: Am. J. Cancer, 1934, 22, 620. LUBARSCH: in Henke-Lubarsch: Handb. d. spez. path. Anat., vol. 6, pt. 1, p. 587, Berlin, 1925. WELLS: Arch. Surg., 1922, 5, 356 (Epidermoid cancer and stone). WOLLSTEIN: Arch. Path., 1927, 3, 1 (Wilms' tumor).
- Tumors of the Renal Pelvis.** SCHOLL: Surg., Gynec. and Obst., 1924, 38, 186.
- Tumors of the Urinary Tract.** HUEPER, *et al.*: J. Indust. Hyg. and Toxicol., 1938, 20, 46. SEMPRONJ AND MORELLI: Am. J. Cancer, 1939, 35, 534.
- Uremic Enteritis.** JAFFÉ AND LAING: Arch. Int. Med., 1934, 53, 851. STREICHER: Arch. Int. Med., 1928, 42, 835.
- Urinary Calculi.** ALBRIGHT, *et al.*: J. A. M. A., 1934, 102, 1276. ANDERSON: Proc. Staff Meetings, Mayo Clinic, 1946, 21, 326. COUNSELLOR AND PRIESTLEY: J. A. M. A., 1935, 104, 1309. RANDALL: Surg., Gynec. and Obst., 1937, 64, 201.
- Vacuolar Nephropathy.** ANDERSON: South. M. J., 1941, 34, 257. KULKA, *et al.*: Am. J. Path., 1950, 26, 349.
- Wilms' Tumor.** MASSON: Am. J. Cancer, 1938, 33, 1.

## Chapter

## 25

### THE MALE REPRODUCTIVE SYSTEM

#### THE TESTICLE AND EPIDIDYMIS

##### INFLAMMATION OF THE TESTICLE AND EPIDIDYMIS

THE testicle and epididymis form one organ although they are developed separately. Inflammation may be practically confined to the epididymis as in gonorrhea, or to the testicle as in the orchitis of mumps.

**Gonorrheal Epididymitis.**—Gonorrhea commences as an acute urethritis, with marked inflammatory change in the subepithelial connective tissue. The infection ascends the urethra and settles in the posterior urethra. The disease may clear up after an acute course of a few weeks, or the infection may linger in the posterior urethra and affect other parts of the genital tract. The epididymis is the chief sufferer, infection occurring usually in the second and third months. The first lesion is at the lower pole, the globus minor, but soon the whole organ is involved. It is seldom that the infection spreads to the testicle, although inflammation of the surrounding fibrous tissue may make that organ feel enlarged and hard. The epididymis is swollen and tender. Hydrocele is often present, and there may be some thickening of the spermatic cord. The type of inflammation is unusual. As the gonococcus is a pyogenic organism, there is suppuration with the formation of minute abscesses, yet there is no extensive abscess formation as might be expected, but rather a widespread inflammatory edema. The inflammation is acute and subsides quickly, but often leaves fibrous scars which obliterate the seminiferous tubules. Fortunately the epididymitis is usually unilateral. When it is bilateral, complete sterility may result.

Other gonorrheal lesions are prostatitis, stricture of the urethra, and blood infection of distant organs. The first two are considered below. Blood infection may give rise to inflammation of joints (gonorrheal arthritis) and of tendon sheaths (tenosynovitis).

**NON-GONORRHEAL EPIDIDYMITIS.**—Non-gonorrheal epididymitis is very much less common. It is usually caused by staphylococci, sometimes by streptococci or *Bacillus coli*. The infection is secondary to stricture of the urethra, enlarged prostate, or inflammation of the seminal vesicles. There is abscess formation in the epididymis, marked hardness and thickening of the vas and seminal vesicle, and a tendency to chronicity and recurrences.

**Orchitis.**—Inflammation of the testicle may be due to trauma or to acute infections. *Traumatic orchitis* is caused by a blow, which is followed by acute inflammatory edema of the organ. The condition is short and

acute, but sometimes results in atrophy of the testicle. *Metastatic orchitis* is the term applied to infection from the blood stream which occurs in certain acute fevers. It is usually due to mumps, occasionally to typhoid fever and smallpox, and rarely to other febrile and septic conditions. Sometimes the *orchitis of mumps* has preceded the parotitis. It is usually unilateral, and is rarely seen before the age of puberty, being commonest in young men. The enlargement is not great owing to the firm fibrous tunica albuginea, but the tension is great and the pain correspondingly severe. The epididymis is rarely involved. The chief lesions are early edema, followed by diffuse lymphocytic infiltration of the interstitial tissue with focal hemorrhage, destruction of the germinal epithelium, and plugging of the tubules by epithelial debris and fibrin (Gall). The lesion is never suppurative, but may be followed by fibrosis and atrophy of the testicle. Infection of *extension* from the posterior urethra may occur. In severe gonorrheal epididymitis there may be slight involvement of the testicle. There may be colon bacillus infection from a cystitis. In these cases the lesions are suppurative.

### TUBERCULOSIS OF THE GENITAL TRACT

As the entire genital tract, sometimes indeed the urogenital tract, may be involved by tuberculosis, it is convenient to consider all the organs together. The infection is usually blood-borne, and starts in the lower pole of the epididymis (Fig. 348), but occasionally in the seminal vesicle. In a small proportion of cases the bacilli spread along the vas from the bladder, which itself is infected from a focus in the kidney. Nodules are formed throughout the epididymis, so that the organ is enlarged and hard. Caseation and liquefaction occur sooner or later, the skin of the scrotum is involved, and a tuberculous fistula is formed. By the time the patient is seen clinically the disease has usually spread throughout the genital tract, so that the vas, seminal vesicles, and prostate are all involved. The *testicle* is not involved early, but in time the disease spreads to it from the epididymis, invading first the body of Highmore. The *spermatic cord* is thickened and nodular. The *seminal vesicle* is involved early, and indeed the infection may commence there. The entire vesicle is usually destroyed. The *prostate* may be infected either from the genital tract or from the kidney. Caseous nodules are formed in the gland with destruction finally. The *tunica vaginalis* may be studded with tubercles, so that a hydrocele is a common accompaniment. The *other epididymis* is often involved at a



FIG. 348. — Tuberculosis of the epididymis. There is a caseous area in the lower pole and the spermatic cord is thickened.

later stage, probably by way of the lymphatics. The *bladder* shows tuberculous ulcers, especially in the trigone. The *kidneys* are occasionally involved by upward spread from the genital tract, but combined genito-urinary tuberculosis usually originates in the kidney, with secondary infection of the genital tract.

### SYPHILIS OF THE TESTICLE

Syphilis of the testicle has ceased to be a frequent lesion. Unlike tuberculosis it affects the body, seldom the epididymis. It occurs in two forms which may be combined: (1) a diffuse interstitial inflammation, and (2) a gumma. (1) The *diffuse form* is the commoner, although usually overlooked because it gives rise to no symptoms. The testicle is not enlarged or tender, but it has a characteristic wooden hardness owing to diffuse fibrosis, and there is a loss of the normal testicular sensation when the organ is squeezed. The tunica albuginea is thickened, and the gland is pervaded with white bands of fibrous tissue, so that the cut surface remains flat instead of bulging forward in the normal manner. Microscopically there is at first a diffuse formation of cellular inflammatory tissue containing many spirochetes, followed later by fibrosis with atrophy and disappearance of the tubules. (2) A *gumma* causes enlargement of the testicle. It is at first gray, but later becomes white and fibrous. Softening is uncommon, and the lesion tends to become scarred.

### TUMORS OF THE TESTICLE

Great differences of opinion exist regarding tumors of the testicle. These cannot be discussed here, and the tumors will simply be divided into two groups without an attempt at justification. For a discussion of the various views the reader is referred to books devoted to tumors. The two groups into which practically all the testicular tumors fall are the seminomas and the teratomas, of which the former are the commoner. Many workers believe that the seminoma arises from the germinal cells of the seminiferous tubules (hence the name). It seems rather better to regard all testicular tumors fundamentally as teratomas, which may be divided into the simple and the complex. The simple teratomas are more or less homogeneous tumors, which only possess representatives of one primordial germ layer; they include the seminomas. In support of this idea is the fact that one occasionally sees seminomas with cartilage and other structures. Complex teratomas include embryoma and chorionepithelioma. An argument in favor of the teratomatous nature of testicular tumors is the fact that the great majority occur in early adult life, whilst 90 per cent occur before the age of fifty.

**Seminoma.**—Ewing calls this tumor an embryonal carcinoma. It grows slowly and replaces the testicle. The cut surface is fleshy and homogeneous so as to resemble that of a sarcoma. The *microscopic picture* is variable. The cells may be large and clear like spermatocytes, or may be small and dark like the cells of a lymphosarcoma. The arrangement may be tubular in the most slowly-growing tumors, but diffuse in the rapidly-growing ones (Fig. 349). It is evident that the tumor may closely resemble either a sarcoma or a carcinoma. The seminoma of the testicle is homolo-

gous with the dysgerminoma of the ovary; they are of similar appearance, and both originate from the early stages of germ cells.

**Teratoma.**—This is a teratoid tumor which probably arises from a germinal blastomere or primitive germinal cell. As these cells are totipotent the tumor may contain structures derived from three embryonic layers. It is also called embryoma, mixed tumor of the testicle, and, in the older literature, fibrocystic disease. The tumor may attain a very great size. The cut surface usually presents a characteristic cystic appearance (hence the old name of fibrocystic disease), the cysts varying much in size in different specimens and sometimes being absent. The *microscopic appearance* is extremely varied, though in some cases the growth is almost confined to one

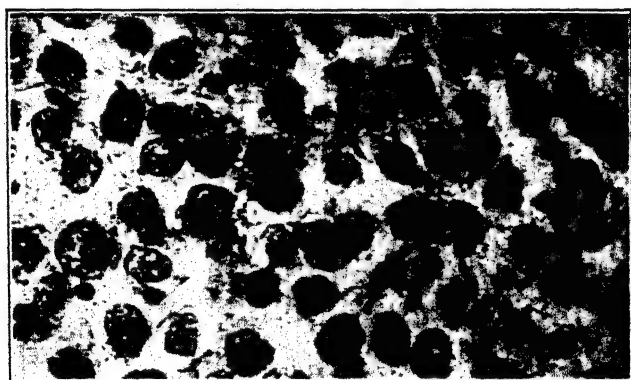


FIG. 349.—Seminoma. The cellular arrangement is anaplastic. The cytoplasm has for the most part disintegrated; only nuclei and nucleoli are seen.  $\times 600$ .

type of tissue. From the *mesoderm* there may be cartilage, bone, plain and striated muscle, fat and lymphoid tissue; from the *entoderm* there may be tubular spaces lined by columnar cells, i.e., abortive attempts at forming an alimentary canal; from the *ectoderm* there may be stratified epithelium with typical cell nests. It is easy to understand how the tumor may be mistaken for a chondroma, myxosarcoma, adenocarcinoma, epidermoid carcinoma, lymphosarcoma, etc. A usual appearance is a mixture of lymphoid tissue, cartilage, and tubular spaces, many of which are dilated to form cysts of varying size (Fig. 350). The picture may be that of an *embryonal adenocarcinoma*, in which there is the formation of acini lined by cuboidal or low columnar cells in addition to solid masses of cells.

Both the seminoma and teratoma are malignant tumors, although the latter may show no malignant characteristics for a considerable time. There is lymph spread to the abdominal lymph nodes, and blood spread to the lungs, liver, and other viscera.

By far the most extensive series of testicular tumors analyzed is that of Friedman and Moore, comprising 922 cases. Their nomenclature differs from that employed here, being seminoma (35 per cent), teratocarcinoma (35 per cent), embryonal carcinoma (19 per cent), teratoma (7 per cent),

and miscellaneous (4 per cent). Half of their teratoid neoplasms which metastasized gave rise to teratocarcinomatous tumors and half to pure embryonal carcinomas. They found that the seminomas had a better immediate prognosis than the other malignant tumors. They consider that the seminomas are tumors of primordial germ cells, whereas the other tumors are composed of differentiating trophoblastic tissues.

An important though puzzling feature of malignant tumors of the testicle is the occurrence of a positive Aschheim-Zondek test in the urine. The reaction is much the most marked in chorionepithelioma (see below), but it may also be present in other testicular tumors. It seems probable that the tumor produces a hormone which stimulates the anterior pituitary to secrete an increased amount of prolactin. It is said that the anterior lobe of the pituitary shows hyperplasia of the basophilic cells.



FIG. 350.—Embryoma of testicle. The structure is very varied showing tubular structures, cystic spaces, and cartilage in the center.  $\times 30$ .

**CHORIONEPITHELIOMA.**—This rare tumor is a special development of a teratoma in which fetal membranes have been formed, the chorionic epithelium giving rise to the chorionepithelioma. Other structures are also formed, but these tend to be destroyed by the malignant growth. In one case which I studied, typical choroid plexus was present. The tumor usually remains small, and its structure may be obscured by hemorrhage so that it is easily overlooked. The primary tumor may be only a few millimeters in size, but large secondary growths are formed in the lungs, liver, etc. The Aschheim-Zondek test is positive. Gynecomastia (female type of breast development) is common.

**INTERSTITIAL-CELL TUMOR.**—This is a rare tumor which is met with both in man and the lower animals. It tends to be light brown in color. The cells of which it is composed are arranged in solid masses supported by a minimal amount of delicate connective tissue. They are polygonal, intensely acidophilic, and may present a foamy vacuolated appearance owing to the presence of fat. When the tumors develop before puberty there is evidence of sexual precocity, but when they occur at a later period there may be impotence, gynecomastia, and a positive Aschheim-Zondek reaction due to excess of estrogen. They are of slow growth, and are either benign or of a low grade of malignancy. Similar tumors can be induced in mice by the administration of estrogen.

**TUBULAR ADENOMA.**—This benign tumor occurs in the undescended testis. As it apparently arises from Sertoli cells it might well be called *Sertoli cell tumor*. The majority of the cases in the literature are examples of Sertoli cell hyperplasia rather than true tumors.

**TESTICULAR TUMORS AND SEX HORMONES.**—Either masculinizing or feminizing effects may be produced by tumors of three organs: the testes, ovaries and adrenals. As a rule such tumors are rich in lipid, and therefore yellow in color. Feminization in men may be caused by a rare tumor homologous with the ovarian arrhenoblastoma (Teilum). An adrenal cortical tumor may produce both estrogenic and androgenic substances. This is not so strange as might appear at first sight, for there is a very close chemical relationship between the steroid compounds which constitute the male and female sex hormones. A cynic, indeed, has suggested that the only essential difference between Romeo and Juliet was an—OH linkage. Moreover steroids which produce an estrogenic effect are not necessarily identical with estrin.

The presence of the chorionic type of gonadotropin in the urine in a case of testicular tumor indicates that the tumor contains chorionic tissue, for the hormone is only produced by such tissue. (The chorionic type must be distinguished from the castrate type of gonadotropin; the latter, which is produced by the pituitary, occurs in the urine of castrates and of elderly men and women.) Although chorionic gonadotropin may be present in the urine, no chorionic tissue may be found in the tumor. In such a case it is probable that if the entire tumor had been examined microscopically, such tissue would have been discovered. In one such case the metastases alone showed chorionepithelioma (Brewer).

## THE PROSTATE

### INFLAMMATION OF THE PROSTATE

Prostatitis may be acute or chronic. Both forms are usually due to gonococcal infection. The *acute* form is part of an acute posterior urethritis. It is usually mild in type, but some abscesses may be formed, and occasionally there is extensive suppuration. In *chronic* prostatitis foci of chronic inflammatory cells are scattered through the gland, with varying degrees of fibrosis. The prostate is hard, and may be larger or smaller than normal, depending on the amount of scarring which has taken place. In these chronic cases there is often a mixed infection with *Bacillus coli*, staphylococci, etc.

### HYPERTROPHY OF THE PROSTATE

Enlargement of the prostate is very common in men over the age of sixty years, but only in a small number of cases (about 8 per cent) does it cause symptoms. It is essentially a disease of advancing years, and is hardly ever seen in early life. The reason of the hypertrophy is uncertain. It is probably an expression of imbalance of the sex hormones in the male, analogous to cystic hyperplasia of the breast. When estrin is injected into castrated rats there is hyperplasia of epithelium, smooth muscle and connective tissue. These changes do not occur if testicular extract is injected at the same time, nor in normal rats which have not been castrated. This suggests that prostatic hypertrophy in elderly men is due to a disturbance



in the balance between the production of testicular hormone and that of estrin (also produced by the testicle). It may be noted that the prostates of children at birth often show similar changes, probably due to estrin from the placenta. The hope is that in the future it may be possible to control prostatic hypertrophy by means of hormone therapy.

The condition of the prostate varies, depending on the proportion of glandular to fibrous tissue, so that it may be large and soft or relatively small and hard. Usually the enlargement is made up of a series of rather spongy nodules with clearly-defined margins; these nodules are clearly seen on the cut surface. Moore emphasizes the marked difference between the lobular architecture, both gross and microscopic, of the normal prostate

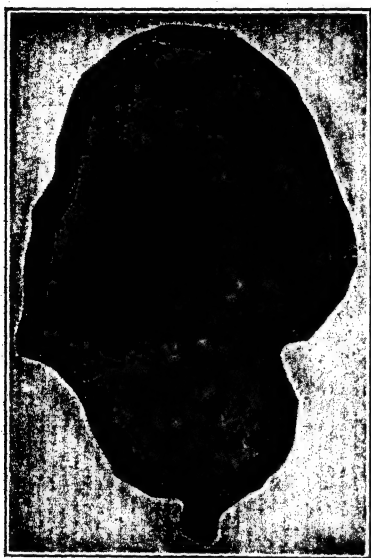


FIG. 351.—Hypertrophy of the prostate. The gland is considerably enlarged, and the middle lobe projects up into the bladder, the wall of which is hypertrophied.

and the nodular character of benign hyperplasia. The part of the gland containing the nodules enlarges so as to form a mass which compresses the surrounding tissue, and this in turn constitutes a false capsule which enables the nodular mass to be separated and shelled out with comparative ease. In other cases there is diffuse fibrosis rather than nodular hyperplasia, in which case no nodules can be seen and shelling out is impossible. The lateral lobes may be enlarged or a new *middle lobe* may be formed by hypertrophy of the group of glands which lies in the floor of the urethra. This middle lobe forms a conical mass which projects up from the floor of the bladder, carrying the urethral orifice with it (Fig. 351).

The *microscopic appearance* is one of glandular hyperplasia with overgrowth of fibrous tissue and muscle in varying degrees (Fig. 352). The picture may closely resemble that of lobular hyperplasia of the breast.

The glandular tissue is increased, the acini are enlarged, and papillary processes of epithelium may project into the lumen. In other cases the glandular tissue is not hyperplastic, but there is a great increase of fibrous tissue and a good deal of plain muscle. Moore, whose studies of the structural variations of the normal prostate are so valuable, considers that the most striking feature of benign hyperplasia is the variation in appearance of the same structure in different parts of the prostate, compared with the uniform appearance of the normal prostate. As infection is a frequent complication, inflammatory foci may be scattered through the stroma.

*Infarcts*, either recent or healed, are frequently found. Although these are small areas of coagulation necrosis similar to what is seen in infarcts

elsewhere, there is no proof that they are due to vascular occlusion. At the margin of the healing infarcts can be seen solid masses of squamous epithelium (Fig. 353). This is a *squamous metaplasia* secondary to the necrosis, and must on no account be mistaken by the pathologist for epidermoid carcinoma, a tumor which is extremely rare in the prostate.

**Effects.**—Enlargement of the prostate is usually unaccompanied by symptoms. The symptoms when present are due entirely to the position of the gland at the urinary outlet. The effects are felt on the urethra, the bladder, and the kidneys. (1) The *prostatic urethra* may be elongated, compressed to a mere slit, and rendered tortuous. This is the most im-



FIG. 352.—Hypertrophy of the prostate. There is marked epithelial proliferation in the acini and ducts.  $\times 60$ .

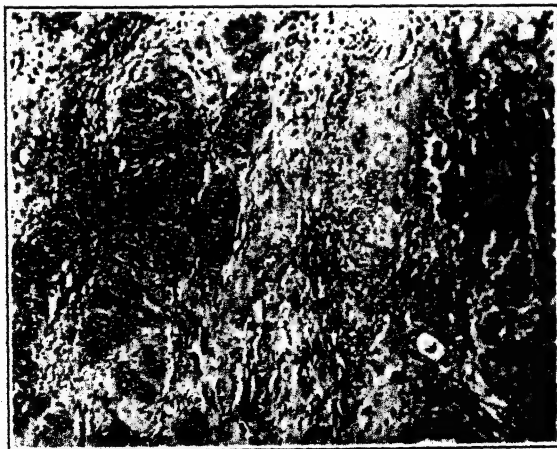


FIG. 353.—Infarct of prostate (right) with squamous metaplasia (left).  $\times 110$ .

portant cause of obstruction. (2) The *bladder* cannot be completely emptied, because the urinary outlet is lifted up above the surrounding floor and the enlarged middle lobe may exert a ball-valve action. Moreover the vesical sphincter is rendered incompetent through being stretched by the middle lobe which grows up from the floor of the urethra. There is therefore a constant dribbling of urine, and yet the bladder is never empty. The residual urine is readily infected and cystitis results. The bladder becomes hypertrophied in its efforts to overcome the obstruction, and the thick bands of muscle give the wall a ribbed appearance. Later there is dilatation, with pouching of the wall between the bands producing false diverticula. Owing to the cystitis and the stagnation of urine, phosphatic calculi are often formed in the bladder. (3) The *kidneys* suffer because of the obstruction and infection. The ureter and renal pelvis on both sides are dilated, so that hydronephrosis is produced. Infection ascends the dilated ureters, and causes pyelonephritis and pyonephrosis. Renal insufficiency now declares itself, non-protein nitrogen is retained in the blood, and the patient dies of uremia. The back-pressure on the kidney is associated with arterial hypertension, even though the kidney damage is only slight. When drainage of the bladder is established there is a marked fall in the systolic blood pressure within forty-eight hours.

Chapman sounds a word of warning which deserves repetition: "It is certainly unjustifiable to remove the prostate merely because it is enlarged and has been associated with some urinary symptoms. This fact should be made clear to the medical student. Prostatic enlargement should be regarded, like the arcus senilis of the cornea and the graying and thinning of the hair, as an anatomical feature of old age which occurs often enough to be regarded as a variety of the normal. Only when obstruction to the flow of urine is produced does it become a disease."

### CARCINOMA OF THE PROSTATE

Cancer of the prostate is the third most common cause of death from cancer in the male. It is often associated with prostatic hypertrophy, but the two conditions occur at the same age period, and there is no proof that there is any etiological relationship between them. About 80 per cent of cancers start in the posterior lobe. This part of the organ is not involved by hypertrophy, and it is left behind after the operation of enucleation, so that the patient may well develop carcinoma though he believes that his prostate has been completely removed. The sedimentation rate is increased in carcinoma but not in benign hypertrophy. The prostate may or may not be enlarged when the patient is first seen, but its chief characteristic is its hardness. It cuts with the gritty sensation of a scirrhus cancer of the breast. The cut surface is dry, does not bulge, is not nodular or lobulated, and shows little yellow islands of carcinoma cells like those seen in a scirrhus cancer of the breast. In all these respects it differs from prostatic hypertrophy. At the same time it must be pointed out that in some cases the gross differentiation is impossible, and that microscopic examination of a number of blocks may be necessary before cancer can be excluded, as the malignant process may be confined to a small part of the gland. Every prostate removed for hypertrophy should be cut up into a series of thin

slices and examined for areas of malignancy indicated by increased hardness and lessened elasticity. In routine microscopic examination of the prostate at autopsy Rich found 14 per cent of carcinoma in men of fifty years of age. In many of these the tumor was only a few millimeters in size, so that even if the patient had lived it might not have produced symptoms for a long time. Moore reports 52 cases of occult carcinoma, in only 10 of which could a gross diagnosis be made. It is important to bear in mind that the incidence of occult, or better, latent carcinoma, is much higher than the mortality.

The *microscopic picture* is adenocarcinoma of varying degree of differentiation. The acini may be so well formed that they are easily mistaken for normal acini (Fig. 354), but they lack the sling of muscle which surrounds each normal gland, so that nests of small acini seem to be invading the stroma which is frequently dense and scirrhus. The cells seldom show anaplasia, and mitotic figures are few or absent. The atypical pattern of the acini is more important than cellular abnormality.

The *spread* is important. Because of early spread the prognosis is bad, but not nearly so bad as it used to be because of better surgical removal and of the ability of therapy with sex hormones to hold the disease in check for

a number of years. The spread is both local and distant. The growth usually starts in the posterior part of the gland and spreads up along the line of ejaculatory ducts; it appears between the bladder and the seminal vesicles where it can be felt on rectal examination. The floor of the bladder and the surrounding fibrous structures are invaded. An important method of spread is along the perineural lymphatics, which can often be seen distended with cancer cells. Perineural invasion of the capsule is one of the earliest changes, no matter how small the primary tumor may be. Bilateral sciatica in an elderly man is strongly suggestive of carcinoma of the prostate. The pelvic and lumbar lymph nodes are involved early, and there may be lymph spread to the thoracic and even the supraclavicular nodes. The inguinal nodes are involved in about 15 per cent of cases, probably due to lymphatic connection with the seminal vesicles and urethra



FIG. 354.—Carcinoma of the prostate. This glandular type may be mistaken in its early stages for simple hypertrophy.  $\times 200$ .

and retrograde transport from these areas. It is evident that hardly a node in the body may escape. Metastases are formed in the liver, lungs, etc., by blood spread. But the commonest distant metastases are in the bones. In about 70 per cent of autopsies the skeleton is found to be involved. The pelvis and lumbar vertebræ are the commonest sites, followed by femur and ribs. Spread to the sacrum and lumbar vertebræ may in some cases be by way of the perineural lymphatics, but, as Batson has pointed out, a more frequent route is probably the vertebral system of veins. When an elderly man is found to be suffering from a tumor of bone, the prostate should always be examined. Moreover the bone metastases in cancer of the prostate are different from those in other secondary carcinomas; the former are sclerosing in type, while the latter are rarefying, a distinction which can be readily recognized radiologically.

**SEX HORMONES AND PROSTATIC CARCINOMA.**—The development and activity of the prostate is dependent on stimuli from the testes. Castration before puberty prevents development of the prostate, and castration in adult life causes regression of the normal gland and decrease in size in cases of prostatic hypertrophy. Huggins and his associates have applied these facts to the problem of the control of cancer of the prostate with remarkable results. Orchidectomy is followed not only by an astonishing improvement in the subjective condition (bone pain, etc.), but also by such objective evidence as a great and permanent fall in the acid phosphatase in the blood and a shrinkage of the primary lesion. Injection of large amounts of estrogen has a similar effect on the acid phosphatase and to a lesser extent on the physical condition, owing apparently to neutralization of androgens which have an opposite effect. The estrogen has a marked effect on the cancer cells, which are either vacuolated due to accumulation of glycogen or may be actually necrotic.

A direct relationship between carcinoma of the prostate and male gonadal activity is revealed by studies on the enzyme *phosphatase*. For long it has been known that phosphatase is found in abundance in growing bone and cartilage. It is also present in the circulating blood, and in certain of the osteodystrophies, particularly Paget's disease, the level in the blood is markedly raised. Two varieties of the enzyme can be distinguished, alkaline phosphatase with an activity maximum at pH 9, and acid phosphatase with an activity maximum at pH 5. The *alkaline phosphatase* is that present in growing bone and is apparently produced by osteoblasts; the only conditions in which it is known to be increased in the blood are certain types of bone disease (especially Paget's disease) and liver disease. The level in the blood may be raised in prostatic cancer owing to bone involvement by metastases. The *acid phosphatase* was originally found in the spleen and kidney of swine and cattle, but far the greatest concentration is in the prostate where it is apparently produced by the prostatic epithelium. A similarly large amount is found in carcinoma of the prostate. The enzyme can be demonstrated microscopically in the epithelium of both the normal and malignant gland by Gomori's method. In cases where the carcinoma is disseminated in the bones, particularly the bony pelvis, there is a marked rise in the acid phosphatase in the serum. Such a rise has been observed in no other condition. Huggins and his associates claim that when acid phosphatase is present in activity greater than 10 units in 100 cc. disseminated prostatic cancer is present. The increase in the blood is not found in every case.

Finally, there appears to be a relationship between the pituitary-adrenal axis and cancer of the prostate. Bilateral adrenalectomy in selected cases has resulted in remarkable improvement, particularly in relief of the distressing and intractable back pain.

**SARCOMA.**—Sarcoma of the prostate is very rare. It is probable that most of the tumors which in the past have been called sarcoma are examples of anaplastic, undifferentiated carcinomas.

**PROSTATIC CALCULI.**—Prostatic calculi may form in the ducts of the gland. They are usually minute and give rise to no symptoms.

## PENIS AND SCROTUM

### CARCINOMA OF THE PENIS AND SCROTUM

*Cancer of the penis* begins on the glans or prepuce. The tumor shows a striking geographical distribution, being rare in the Americas and Europe, but common among the Chinese, Malays, African Negroes, and in India. The disease is unknown in persons such as Jews who have been circumcised in infancy. It is rare in Mohammedans who are circumcised later (3 to 14 years). Circumcision in adolescence or adult life offers little protection, as the damage has apparently been done. In over 70 per cent of cases phimosis is or has been present, with retention of smegma which probably acts as a carcinogen. The lesion takes the form of a small wart at first, but a large fungating mass is formed later. The tumor is an epidermoid carcinoma. Secondary growths occur in the inguinal and later in the retro-peritoneal lymph nodes. Blood spread is later still. *Cancer of the scrotum* used to occur in chimney sweeps and still does in workers handling coal tar and paraffin, owing to the long-continued action of these carcinogenic substances.

### HYDROCELE

A hydrocele is a collection of fluid in the tunica vaginalis. It may be acute or chronic in type. The *acute* cases are due to spread of infection usually from the epididymis, occasionally from the body of the testicle, to the tunica vaginalis. The two infections commonly associated with acute hydrocele are gonorrhea and tuberculosis. The fluid, which is moderate in amount and somewhat turbid owing to the presence of pus cells, accumulates rapidly. The *chronic* variety is probably due to some low-grade infection, but this is not susceptible of proof. The fluid is clear and watery, rich in albumin, and may be so abundant as to cause great distention of the scrotum. It may contain shimmering cholesterol crystals, and in some cases fibrinous bodies may separate out. The sac tends to become greatly thickened, especially if there has been repeated tapping. In long-standing cases the pressure on the testicle may lead to atrophy.

*Encysted hydrocele of the spermatic cord* is a collection of fluid in an obliterated portion of the processus vaginalis between the testicle and the internal abdominal ring. It does not communicate with the tunica vaginalis.

**Hematocoele.**—Hematocoele is the name given to a hemorrhage into a hydrocele. The hemorrhage is usually due to trauma of some kind. This may be a direct blow or kick, or it may be the result of tapping the hydrocele. In the latter case there is either injury to a vein by the needle, or the sudden reduction of pressure outside an unsupported vessel may cause it to give way. Sometimes the hemorrhage may occur spontaneously. The

cavity of the tunica vaginalis is occupied by breaking-down blood clot, and the walls are covered by ragged deposits of fibrin.

### SPERMATOCELE

A spermatocele is a cystic dilatation of the spermatic ducts of the epididymis. The cyst is single or multilocular, and is situated at the upper end of the testicle. The fluid, which contains hardly any albumin, is of a peculiar milkiness owing to the presence of great numbers of spermatozoa.

### VARICOCELE

This is a varicosity of the pampiniform plexus of veins in the spermatic cord. There is a primary and a secondary form. The *secondary* form is due to pressure on the spermatic vein, usually by a tumor of the kidney because of its proximity to the termination of that vein. It therefore is commoner over middle age. The *primary* form is very much more frequent. It is called primary because the cause is unknown. It is common in young unmarried men, and may be related to the congestion caused by unrelieved sexual stimulation. It is nearly always on the left side, so that a varicocele on the right side should suggest the presence of a tumor. The left spermatic vein enters the renal vein at right angles; the right spermatic vein enters the vena cava obliquely. There is therefore more resistance to the outflow of blood from the left vein. A loaded rectum may also press on the left vein. The veins of the plexus are elongated, tortuous, and feel like a bag of worms. They empty when the patient lies down. Thrombosis is rare.

### OTHER LESIONS OF THE PENIS AND SCROTUM

**PHIMOSIS.**—Phimosis or narrowing of the prepuce is a congenital condition. In the more severe cases there may be marked urinary obstruction with hypertrophy of the bladder, dilatation of the ureters and hydronephrosis. The relation to carcinoma has already been mentioned.

**CALCAREOUS DEPOSITS.**—Calcareous deposits in the penis may occur in old people. They correspond to formations of bone in the lower animals.

**SYPHILIS.**—The primary chancre of the penis has already been described in Chapter 7. A primary chancre sometimes occurs in the scrotum, but secondary lesions (condylomata) are much more frequent. The scrotum may be involved in a gumma of the testicle.

**CONGENITAL ANOMALIES.**—*Undescended testicle* is a condition in which the testicle is arrested at some point in its descent. This may be in the neighborhood of the kidney, at the internal abdominal ring, in the inguinal canal, or at the external abdominal ring. The inguinal canal is much the commonest position. Here the testicle is exposed to trauma and therefore liable to attacks of orchitis. An undescended testicle is unusually prone to develop a malignant tumor. The gland is atrophic and the spermatogenic cells disappear, so that if the condition is bilateral the person is sterile. Virile power is retained, however, for the interstitial cells of Leydig do not share in the atrophy; indeed, they often appear to be more numerous than usual, and the best place to see these cells is in an undescended testicle (Fig. 355). Cryptorchism (non-descent of testicle) is now known to be due in some cases to lack of the gonadotropic hormone of the anterior pituitary which regulates the process. Administration of the hormone may be followed by descent of the testes.

Curiously enough the gonadotropic hormone is present in the urine of these boys and disappears under the treatment (Hess). It is known that when the testes have been removed (or are undescended) there is an excessive secretion of gonadotropic hormone. *Epispadias* is incomplete closure of the urethra on the dorsal aspect of the penis. *Hypospadias*, which is more common, is the same condition on the ventral aspect. *Hermaphroditism* is a blending of the male and female sexual organs. In very rare cases testicles and ovaries have been present together. The usual arrangement is for the gonads of one sex to be associated with the secondary sexual characters of the other. The commonest form is that in which the scrotum is split so as to resemble the labia majora, the penis is rudimentary, the testicles are undescended, and the secondary sex characters are of the female type.



FIG. 355.—Hypertrophy of interstitial cells in undescended testicle.  $\times 100$ .

#### ADDITIONAL READING

- Carcinoma of Prostate.** BARON AND ANGRIST: *Arch. Path.*, 1941, **32**, 787. DEAN, *et al.*: *Surgery*, 1944, **16**, 169. GOMORI: *Arch. Path.*, 1941, **32**, 189. HUGGINS AND HODGES: *Cancer Research*, 1941, **1**, 293. HUGGINS, *et al.*: *Arch. Surg.*, 1941, **43**, 209. MOORE: *J. Urol.*, 1935, **33**, 224. RICH: *J. Urol.*, 1935, **33**, 215.
- Epithelial Metaplasia in Prostatic Infarction.** MOSTOFI AND MORSE: *Arch. Path.*, 1951, **51**, 340.
- Interstitial-cell Tumor of Testis.** BONSER AND HAWKESLEY: *J. Path. and Bact.*, 1943, **55**, 295. STEWART, *et al.*: *Am. J. Cancer*, 1936, **26**, 144.
- Mumps Orchitis.** GALL: *Am. J. Path.*, 1947, **23**, 637.
- Prostatic Hypertrophy.** BURROWS: *Am. J. Cancer*, 1935, **23**, 490. CHAPMAN: *Lancet*, 1949, **2**, 684. KORENCHESKY AND DENNISON: *J. Path. and Bact.*, 1935, **41**, 323. MOORE: *Am. J. Path.*, 1936, **12**, 599; *J. Urol.*, 1943, **50**, 680.
- Tubular Adenoma (Sertoli Cell Tumor).** STALKER AND HENDRY: *J. Path. and Bact.*, 1952, **64**, 161.
- Tumors of the Testicle.** BREWER: *Arch. Path.*, 1946, **41**, 580. FRIEDMAN AND MOORE: *Mil. Surgeon*, 1946, **99**, 573. GORDON-TAYLOR AND TILL: *Brit. J. Urol.*, 1938, **10**, 1. SCULLY AND PARHAM: *Arch. Path.*, 1948, **45**, 581; 1948, **46**, 229. TEILUM: *Acta path. et microbiol. Scand.*, 1946, **23**, 242, 252.
- Undescended Testicle.** HESS, *et al.*: *J. A. M. A.*, 1937, **108**, 352.



## THE FEMALE REPRODUCTIVE SYSTEM

## THE UTERUS

**MENSTRUATION.**—*Influence of the Ovary.*—The basis for the study of gynecological pathology is an understanding of the changes which the endometrium undergoes during the menstrual cycle. Throughout the entire menstrual cycle of twenty-eight days the endometrium is responding to influences from the ovaries, so that the uterus may be said to be the mirror which reflects ovarian activity. If that activity becomes perverted, the changes in the endometrium will cross the boundary line between the physiological and the pathological.

In the human subject ovulation occurs at the middle of the menstrual cycle, on the thirteenth or fourteenth day from the beginning of the last period. Immediately after ovulation the corpus luteum begins to be formed from the stratum granulosum of the ruptured follicle. The ripening follicle produces one active principle which acts on the endometrium, while the corpus luteum produces quite a different principle with an effect opposite and antagonistic to the follicular one. As soon as the corpus luteum degenerates and becomes functionally impotent, which happens from twenty-four to thirty-six hours before menstruation, the follicular principle, which has been present all the time though suppressed, reasserts itself and continues to do so until the development of the next corpus luteum. It is this resumption of follicular activity which is probably the direct cause of menstruation. If the ovum continues to live on account of being fertilized, the corpus luteum will persist and grow larger, and the amenorrhea (absence of menstruation) of pregnancy is established. The follicular principle is called estrin or theelin, because when the fluid of ripening follicles is injected into an animal it brings on estrus or heat. In pregnancy there is a great overproduction of estrin, the excess appearing in the urine where it can readily be demonstrated. The corpus luteum hormone is called progesterone, because it stimulates premenstrual or pregestational changes in the uterus.

**INFLUENCE OF THE PITUITARY.**—Just as the endometrium seems to be under the influence of the ovary, so the ovary seems to be under the influence of the anterior lobe of the pituitary. The periodicity of the ovary is not inherent in itself, but is dependent on the anterior pituitary which regulates it. The work of Smith and Engle, Zondek and Aschheim, and others, has shown that implants or extracts of the anterior lobe of the pituitary in an immature female animal rapidly bring on a state of maturity or premature puberty. As a result of rapid maturation of the follicles, estrin is formed and this brings on all the phenomena of estrus. No changes are observed if the ovaries are first removed, for a castrated animal does not respond to anterior pituitary stimulation. The pituitary produces a follicle-stimulating hormone (F.S.H.) and a luteinizing hormone (L.H.). In the literature on the subject the term female sex hormone often occurs. This is somewhat confusing, for it may include both the estrus-producing hormone of the ovary (estrin) and the ovary-stimulating hormone of the pituitary. In practice it is usually

reserved for the former. It may be noted that estrin can be obtained from the male pituitary as powerful as that from the female.

*Influence of the Placenta.*—Extracts of placenta produce the same effect on the ovary as extracts of the anterior lobe of the pituitary, first stimulating the follicles and then causing luteinization. During pregnancy there appears in the urine an ovary-stimulating principle, which is the active substance in the Aschheim-Zondek test for pregnancy, and which was formerly thought to be the pituitary hormone, the prolactin of Zondek. It is now believed that no pituitary hormone appears in the urine, and that the effect is due to an anterior-pituitary-like substance produced by the placenta. These considerations do not, however, alter the great practical value of the test. In the original Aschheim-Zondek test the urine was injected into immature female mice, but in the more convenient Friedman modification adult female rabbits are used (the female rabbit ovulates normally only after mating). If the urine is from a pregnant woman, in the course of twenty-four to forty-eight hours the ovaries will show hemorrhagic follicles (Fig. 356), or the even more significant crater from which the ovum is discharged before hemorrhage occurs into the follicle. After delivery the Aschheim-Zondek (or Friedman) test becomes negative in seven to ten days. If it remains positive it indicates retained placenta or the presence of hydatidiform mole or chorionepithelioma. It is positive in tubal pregnancy until tubal abortion destroys the chorionic villi in the tube.



FIG. 356.—Friedman test. The ovary on the left shows hemorrhagic lesions which indicate a positive reaction; that on the right indicates a negative reaction.

The female sexual cycle can be divided into two phases: (1) a *follicular, estrin* or *proliferative phase* from the close of menstruation to ovulation (from about the fifth to the twelfth day), and (2) a *luteal, progesterone* or *secretory phase* from ovulation to about twenty-four hours before the onset of menstruation. We shall find that these two phases are accurately reflected in the ovarian mirror—the endometrium (Figs. 357 and 358). In the estrin phase there is repair of the tissues destroyed during menstruation; in the progesterone phase the endometrium is prepared for an approaching pregnancy (decidual reaction, pseudopregnancy). If the ovum remains unfertilized, all sign of these preparations is removed in the destructive and hemorrhagic process of menstruation.

The *proliferative* or *estrin phase* of the menstrual cycle is of about one week's duration, extending from the end of menstruation to ovulation. It provides the histological picture of what used to be considered the normal endometrium. During this period the endometrium is being acted on by the estrin of the ripening follicle. It grows steadily in thickness, the low epithelium of the postmenstrual stage becomes tall and columnar, mitotic figures are numerous both in the glandular epithelium and the stroma, there may be a pseudostratification of the columnar epithelium which may be several layers thick in some of the glands, and the glands become more and more tortuous, particularly in the deeper part of the endometrium giving it a spongy appearance.

The *secretory* or *progesterone phase* begins after ovulation and formation of the corpus luteum, but the changes are only well developed about five days before menstruation. This is the stage of glandular activity and secretion (not reproduction) and of decidual reaction. The secretory activity of the glands becomes more and more marked, the epithelium which is at first distended with mucin changes from high to low columnar and appears to melt into the mucin which passes into the lumen of the gland. As a result of this activity the glands develop a characteristic spirally twisted



FIG. 357.—Estrin phase.

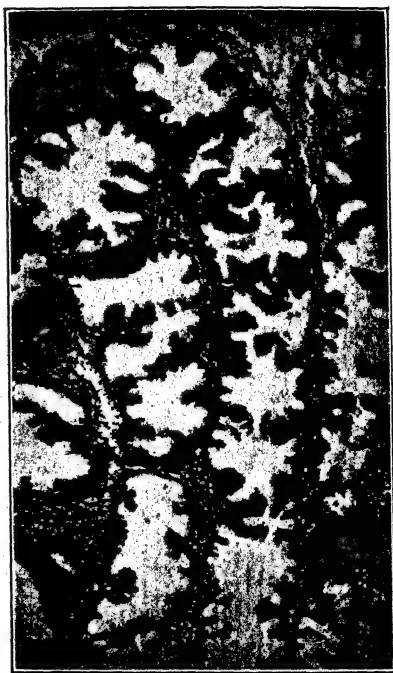


FIG. 358.—Progesterone phase.  $\times 45$ .

FIGS. 357 AND 358.—Endometrial phases.

or corkscrew appearance, and in consequence buds project into the lumen like the teeth of a saw, giving a false suggestion of papillary formation. It is this highly glandular but perfectly normal appearance which in the past was responsible for the very common diagnosis of "glandular endometritis." By this time the endometrium is divided into a superficial compact layer and a deep spongy layer full of spiral glands. The stroma cells of the compact layer undergo the second change that is characteristic of the premenstrual or corpus luteum phase, the oval cells becoming enlarged, rounded, and epithelioid in type, and closely resembling the decidual cells of pregnancy. It is indeed a decidual reaction, for if pregnancy supervenes it is these cells which form the decidua of pregnancy. For this reason it is never safe in medico-legal work to make a diagnosis of pregnancy merely

because decidual cells have been found in uterine scrapings. The decidual reaction has been called a pseudopregnancy. A day or two before menstruation the superficial layer is infiltrated with leucocytes. Widespread necrosis of the tissue on the surface now takes place, the compact layer is cast off, the walls of the capillaries are destroyed, and menstrual bleeding is the result. This necrosis and expulsion of tissue may be regarded as an expulsion or abortion of the pseudopregnancy. If impregnation has occurred and a fertilized ovum reaches the uterus, menstruation does not occur, the decidua-like layer is retained, and developed into the decidua of pregnancy.

It is evident that these endometrial changes are the combined result of the follicular hormone and the lutein hormone. If ovulation fails to occur and no corpus luteum is formed, only the first set of changes will take place. We shall see that this is of profound importance, and that it is one of the principal causes of idiopathic uterine hemorrhage.

Brief reference must be made to changes in the cervix during the menstrual cycle. The cervical secretion is thick and impermeable to spermatozoa, but during the proliferative phase it becomes thin and serous allowing entrance of the sperms at the time of ovulation. Endocervicitis interferes with this adaptive mechanism and thus predisposes to sterility.

### **ENDOMETRIAL HYPERPLASIA AND UTERINE HEMORRHAGE**

Just before or during the menopause a woman may begin to suffer from irregular uterine hemorrhage, which may take the form either of profuse periodic bleeding or of prolonged and continuous bleeding. This irregular hemorrhage may occur at earlier age periods, and sometimes in young women. When the uterus is curetted the endometrium is found to be thick; sometimes it forms papillary excrescences on the surface, and microscopically it presents a markedly glandular appearance. It is now known that the condition is due to ovarian dysfunction (pathological persistence of a ripening follicle), that there is no primary lesion in the uterus, and that the hemorrhage is really functional.

Menstruation is not necessarily dependent on ovulation. In the absence of ovulation there are no cyclic changes in the endometrium, no formation of a pseudopregnancy, but bleeding occurs just the same. This is known as anovulatory menstruation. In the condition under discussion the ovary shows two abnormalities. In addition to being somewhat atrophic, there is an entire absence of lutein tissue, but it does contain one or more ripening follicles. Apparently something prevents ovulation from occurring, and as no corpus luteum is formed the premenstrual changes in the endometrium do not occur. There is a continued overproduction of estrin by the persistent ripening follicle, and the endometrium shows the effect of this overstimulation by manifesting in pathological form the first or hyperplastic phase of the menstrual cycle. It is the absence of the normal secretory "topping-off" caused by progestin which is responsible for the type of endometrium seen in functional hemorrhage. Injection of estrin into animals produces similar changes in the endometrium.

The *endometrium* is markedly thickened, and may measure 15 mm. Sometimes it shows polypoidal protrusions on the surface. *Microscopically* the endometrium presents a highly glandular appearance. The arrangement of the glands is disorderly as compared with the normal vertical extension from base to surface, they are increased in number, there is great variation in size and shape, and the epithelium may be several layers thick (pseudostratification). Some degree of adenomyosis is often present, *i.e.*, an invasion of the muscular wall by the glands of the endometrium;

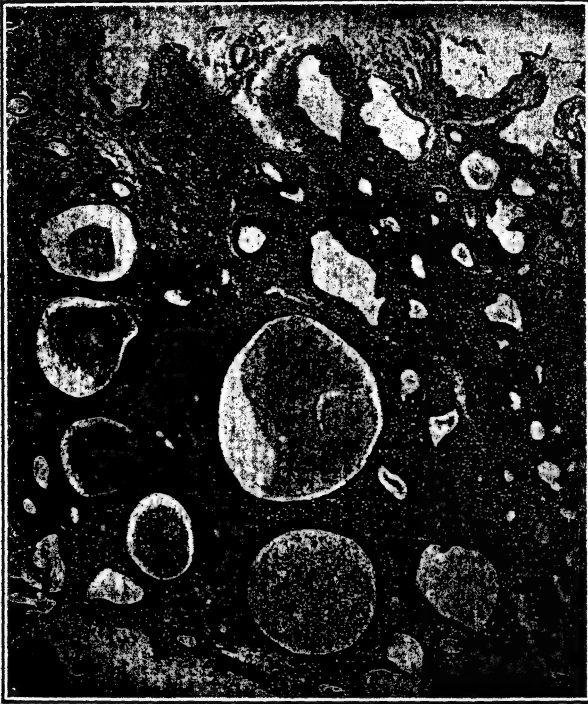


FIG. 359.—“Swiss cheese hyperplasia” of endometrium with marked glandular formation.  $\times 18$ .

this is a minor form of true adenomyoma, which itself is a manifestation of endometriosis. Cystic dilatation of the glands in the deeper layers is common, so as to give what has come to be known as a “Swiss cheese appearance,” and the condition has been called Swiss cheese hyperplasia (Fig. 359). The stroma cells show numerous mitoses, there is extremely marked vascular congestion and a good deal of edema. Decidual reaction is completely absent. If bleeding is going on when the curettage is done, two additional changes will be observed: (1) necrosis of the superficial layers and thrombosis of the small vessels; (2) extensive infiltration with polymorphonuclear leucocytes and mononuclears, but no plasma cells. The necrosis is patchy, not diffuse as in true menstruation. The two most

characteristic features of the microscopic picture are the cystic glands and the patchy necrosis of the surface. The hemorrhage is due chiefly to the local necrosis, but the cause of the necrosis is uncertain. It may be due to cessation of corpus luteum influence as in normal menstruation, or more probably to overstimulation which may lead to thrombosis. To choose a suitable name for the condition is difficult. From the physiological viewpoint it may be called "hyperestrinism," or from the morphological viewpoint "cystic glandular hyperplasia of the endometrium." Its great importance lies in the fact that it is the chief cause of functional uterine hemorrhage. The ovaries commonly present many small follicular cysts and a complete absence of lutein tissue, this being the morphological basis of the hyperestrinism.

*Corpus luteum overactivity* is the converse of the condition just described. The endometrium shows excessive lutein phase changes, even a few days after the middle of the menstrual cycle, and the condition may resemble that of early pregnancy. In these cases the ovaries contain large corpora lutea or excess of lutein tissue.

### ENDOMETRITIS

Acute inflammation of the endometrium may affect the pregnant or non-pregnant uterus. The latter is relatively unimportant. It is commonly caused by the gonococcus, but gonorrhea is chiefly a disease of the cervix, and the infection may pass from there to the tubes producing very little change in the body of the uterus. In acute fevers there may occasionally be an acute endometritis (blood infection), and when the cervical canal is closed by carcinoma the body of the uterus may be distended with pus, a condition of pyometra. Of far greater importance is puerperal endometritis, or acute inflammation of the pregnant uterus during the puerperium.

**Puerperal Endometritis.**—The normal uterus is resistant to infection, but the puerperal uterus is highly susceptible, for the interior presents a raw surface much traumatized and often containing portions of placental tissue separated from their blood supply. Secondary factors such as exhaustion, instrumental interference, hemorrhage, etc., predispose to infection. The infecting bacteria are hemolytic streptococci from the throats of those attending at the delivery or from the patient's genital tract. Milder infections are caused by anærobic streptococci present in the vagina of a large percentage of women at term. The subject of the bacteriology of puerperal sepsis and the mode of infection used to be of supreme importance when the disease used to be the scourge of childbirth before the control of infection by asepsis and antibiotics.

The uterus is soft, flabby and enlarged because normal involution is prevented. The cavity is lined by dirty, breaking-down, necrotic material, under which there is a protective zone of leucocytes. When the infection is mild this zone is wide, and discharge of the infected material is followed by recovery, for blood invasion has not occurred. In the severe streptococcal infections, the leucocytic zone is thin, and the organisms are seen spreading into the deeper parts of the uterine wall. They may reach the

serous coat and set up peritonitis, they may pass along the Fallopian tubes and flood the general peritoneal cavity, or they may spread throughout the body by the blood stream. The large venous sinuses are filled with septic thrombi, which break down and pass into the circulation as septic emboli, setting up pyemic abscesses in the lungs. The blood infection is also responsible for abscesses in the kidneys, joints, etc. An acute endocarditis is a frequent complication. Blood culture is often positive owing to the severe septicemia.

**Endocervicitis: "Cervical Erosion."**—The endometrium of the body of the uterus does not provide a favorable nidus for chronic infection on account of its simple glandular structure and the fact that in large measure it is renewed every month. The reverse is true of the cervix. Here there are no menstrual changes, and the complex racemose glands may harbor infecting microorganisms for long periods. Chronic inflammation of the cervix is accordingly the commonest of all gynecological lesions. By far the commonest cause is laceration of the cervix at childbirth, followed by pyogenic infection. The usual infecting organisms are staphylococci, streptococci, and *Bacillus coli*. Gonorrheal infection of the cervix is the second common cause, but it is of minor importance compared with the first. The gonococcus may infect a laceration, or it may cause infection in a nullipara, as the gonococcus can readily penetrate intact columnar epithelium. The following description applies to the cases which follow laceration.

The infecting bacteria gain entrance to the racemose glands which arise from the columnar epithelium of the cervical canal and penetrate the depths of the muscle. These glands are not seen in the vaginal portion of the cervix which is covered by stratified squamous epithelium. The glands are irritated as the result of the infection, and pour out the thick, viscous, mucopurulent secretion which is characteristic of leucorrhea. It may be said that leucorrhea is almost always a sign of cervicitis. The stroma of the endometrium shows edema and an infiltration with lymphocytes and plasma cells, the latter being the most characteristic cells of chronic inflammation in the female genital tract. In time the inflammation extends to the fibromuscular layer, so that the condition becomes a true cervicitis and not merely an endocervicitis. The columnar epithelium of the surface is curiously resistant and is not desquamated.

Owing to the constant irritation of the infected leucorrheal discharge or for some other reason at present unknown, a patch of squamous epithelium at the external os undergoes maceration and becomes separated, leaving a raw surface which partially or completely surrounds the os. The raw surface is quickly covered by an outgrowth of the columnar epithelium of the cervical canal. The covered patch remains red, however, for the underlying vascular tissue shines through the thin layer of epithelium. This is the condition which has been known in the past as "cervical erosion," a mere clinical nickname for the raspberry red appearance of what used to be thought was a true granulating ulcerated surface. If the cervix has been badly lacerated the os may become everted and patulous. The new epithelium appears to be stimulated by the constant irritation, and gives rise to new racemose glands in the portio vaginalis. This gland formation may

be very marked, so that the condition has been called a proliferative adenoma, and may give to the surface a nodular appearance. In course of time the inflammation dies down, and as a sign of healing the squamous epithelium once more replaces the columnar type over the disputed patch, either by growing under it from the edge or by a conversion of the columnar into the squamous stratified type. The new epithelium tends to close the mouths of the ducts of the new glands, and these may undergo cystic dilations so as to form the bluish swellings on the portio vaginalis known as *Nabothian follicles* (Fig. 360). In some cases the squamous epithelium may



FIG. 360.—Endocervicitis with marked glandular proliferation and Nabothian follicles  
X 16.

grow down into the ducts, forming epithelial plugs which may be mistaken for commencing carcinoma. In the deeper parts of the cervix there is fibrosis and scarring, so that the cervix becomes hard, and owing to contraction of the scar tissue there may be marked eversion of the os.

**PELVIC CELLULITIS (PARAMETRITIS).**—This is a term commonly used by gynecologists. Cellulitis signifies an inflammation of connective tissue due to a wound infection. Pelvic cellulitis may result from infection of lacerations of cervix and vagina occurring during parturition or abortion, or from surgical operations on the cervix. It frequently occurs in conjunction with carcinoma of the cervix. Infection reaches the pelvic cellular tissue either by lymphatics or direct continuity of tissue. The common infecting organism is the streptococcus. Infection spreads in the retroperitoneal fascial planes and there may be abscess formation. While the condition may a long drawn out one, resolution is usually complete and no impairment of reproductive function results.



## SYPHILIS OF THE UTERUS

The cervix is the only part of the uterus affected by syphilis. The lesion may be primary, secondary or tertiary. The primary lesion is a chancre, which can only be diagnosed with certainty by finding the *Spirochæta pallida* with the dark-field method. Many cervical chancres have been diagnosed clinically as carcinoma. The secondary lesion is a mucous patch. The tertiary lesion is a gumma, which may also be mistaken clinically for carcinoma, but can easily be distinguished from it in microscopic sections. All of these conditions are uncommon.

## ENDOMETRIOSIS

This conveniently noncommittal term is used to denote a condition characterized by the formation of endometrium-like masses in a variety of places in the female pelvis and abdominal cavity. As the masses may resemble tumors they are known as endometriomata. The origin of these lesions is a matter of dispute.

It was Sampson of Albany who in 1921 was the first to direct attention to that manifestation of endometriosis which he called endometrial implants. The occurrence of so-called chocolate-colored cysts of the ovary had long been recognized, and lesions of similar structure were found in the rectovaginal septum and other parts of the pelvis. Sampson suggested that these lesions were due to implantation of living endometrial cells on the surface of the ovary, peritoneum, etc. These cells were supposed to be cast into the cavity of the uterus during menstruation, pass along the tubes, and finally settle and grow at the site of the future lesion. The "implant" consists of gland-like spaces surrounded by columnar epithelium, and separated by the cellular stroma characteristic of the endometrium. Hemorrhage occurs at each menstrual period, so that the lesion contains either fresh blood or blood pigment. When the ovarian cyst ruptures the contents are scattered throughout the pelvis together with more desquamated endometrial cells which set up secondary endometrial implants.

Jacobsen's experimental work served to support Sampson's theory. Uterine curettings from rabbits in heat were sowed in the abdominal cavity, and implants were formed in 83 per cent of the animals. Similar results were obtained in monkeys, the implants being identical with those seen in the human patient.

Sampson's views have met both with support and opposition, the latter especially in Germany, where R. Mayer's theory of the serosal origin of the supposed implants is the popular one. The serosal theory, with which the writer is in agreement, is based on the fact that the entire epithelial apparatus of the female genital tract (endometrium, germinal epithelium of the surface of the ovary, etc.) is derived originally from the primitive peritoneum which forms the epithelial lining of the celomic cavity. As the result of ovarian hormonal stimulus the serosa is believed to revert to its original function and form epithelium-lined cavities. Every pathologist is familiar with the fact that as the result of some stimulus such as chronic irritation the flattened serosal cells in either sex may become cuboidal, invade the underlying tissue, and surround gland-like spaces.

## PLATE XIX

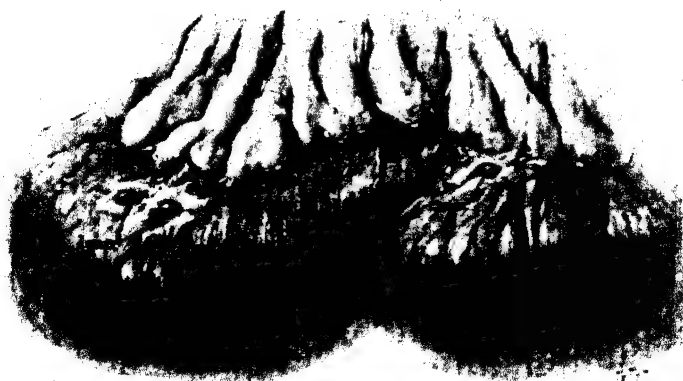
FIG. 1



**Endometriosis (Chocolate-colored Cysts) on Surface of Ovary.**

(John A. Sampson, Surg., Gynec. and Obst., March, 1924.)

FIG. 2



**Endometriosis of Terminal Loop of Ileum.**

(John A. Sampson, Surg., Gynec. and Obst., March, 1924.)

The question of ectopic decidual reaction is of interest in this connection (Weller). A nodular decidual reaction in the subserosa of the appendix is common during pregnancy. Similar lesions are found on the ovary, tube, broad ligament, rectal wall, etc., *i.e.*, a similar distribution to endometriosis. On the appendix the nodules are often mistaken by the surgeon for tubercles. It is evident that under appropriate hormonal stimulation decidual elements may develop from the connective-tissue cells which lie under the serosal cells in the pelvis and lower abdomen. The mesothelial cells of the surface, especially when entrapped in adhesions, appear to form the epithelial elements of endometriosis. Excessive estrin stimulation of the mesothelial and connective tissue is probably responsible for at least many cases of endometriosis, just as it is probably responsible for fibroadenoma of the breast, adenomyoma of the uterus, and possibly uterine fibroids. It may be noted that in all these conditions sterility and uterine hemorrhage are commonly associated features.

The older view that the chocolate-colored blood cysts of the ovary are follicular in origin has been revived by King. It has long been known that some cysts derived from the Graafian follicles, and especially from atretic follicles, may be lined by epithelium which cannot be distinguished from that of the endometrium. This is only natural, as the epithelium of both organs has a common developmental origin. Rupture of a chocolate-colored cyst may be followed by implants on the peritoneum. It is important to realize that the idea of normal adult tissues becoming implanted in other organs and growing there so as to produce irritation is quite without precedent in the science of pathology. Finally it must be recalled that transplantation is not necessary to account for the presence of a tissue at a distance from the normal site of that tissue. Metaplasia will give the same result. It is possible that some of the lesions may be endometrial in origin, some serosal, and some ovarian.

The occurrence of the lesions is confined to the active reproductive period of the patient's life. Removal of the ovaries may be followed by atrophy and disappearance of the lesions. They are said occasionally to undergo malignant change, and Sampson believes that some of the malignant cystadenomas of the ovary arise in this way.

The lesions are most often seen in the *ovary*, where they form one variety of ovarian hematoma, and are commonly known as *chocolate-colored cysts* (Plate XIX, Fig. 1). The cysts, which are close to the surface, are quite small, are lined by columnar epithelium, and separated from one another by the highly cellular stroma so characteristic of the endometrium, in which are embedded many small glands like those of the uterus. There is no plain muscle in the ovary, but in the other lesions this is commonly present. The contents are hemorrhagic, and the blood is renewed at each menstrual period. Rupture of the cysts and liberation of the blood may be followed by the formation of peculiarly dense adhesions which in the past have been naturally thought to be inflammatory in nature.

Similar lesions may occur in the rectovaginal septum. The dense and hard adhesions may be mistaken for a malignant growth in this region. Endometriomata may occur in the Fallopian tubes, the broad and round ligaments, the appendix, the wall of the intestine (Plate XIX, Fig. 2),

the umbilicus, the groin and in abdominal scars after operations on the uterus. Blood may be discharged from an umbilical endometrioma at the menstrual period. Endometrioma of the groin is particularly puzzling. Here the mechanism cannot be that of endometrial implantation. Sampson has shown that endometrial tissue may be found within lymphatics and venous sinuses, and suggests that the cellular masses may spread in the same way as carcinoma, *i.e.*, by the lymph and blood stream as well as by the natural passages (tubes). An inguinal endometrioma may therefore be due to lymph spread. Or it may arise from the remains of an embryological peritoneal process in the inguinal canal, the processus vaginalis (serosal origin).

### TUMORS OF THE UTERUS

**Fibromyoma.**—The tumor known as myoma, fibromyoma and fibroid tumor of the uterus is the commonest of all neoplasms. It is even more frequent in colored than in white women. Although not strictly accurate the condition is commonly called a *fibroid*. The tumors are confined to the reproductive period of life. This suggests that they may bear some relation to ovarian activity. The ovaries are often enlarged, and contain cysts and large unruptured follicles. In the breast the common fibroadenoma, which is often more of a fibroma, is most probably due to abnormal ovarian stimulation. The same may be true of the fibromyomas of the uterus. They never appear after the menopause, and usually tend to retrogress in that period. When estrogenic hormone is introduced under the skin of a guinea-pig in tablet form, uterine fibromyomata are produced; these cease to grow and retrogress when the hormone ceases to act. The tumors occur chiefly in the body of the uterus. Cervical tumors are relatively uncommon.

In its *gross appearance* the fibroid tumor varies considerably. There may be a single tumor or large numbers; they may be very small or very large, and their consistence may be much changed by degeneration. As a rule, the tumor is hard, circumscribed, and the cut surface presents a whorled appearance, due to interlacing bundles being cut in different planes. The more fibrous tissue it contains, the harder and whiter it is, contrasting with the relatively soft and brownish-red surrounding muscle (Fig. 361). As it grows expansively it compresses the muscle and thus forms for itself a capsule from which it can often be shelled out. According to its site the tumor is divided into interstitial, submucous, and subperitoneal varieties. The *interstitial* is the common form, for every fibromyoma commences in the substance of the muscle. It is well supplied with blood from the surrounding muscle, so that degeneration is not very common in this form. The *submucous* fibroid is formed by the centripetal growth of an interstitial tumor. It projects into the uterine cavity, and, owing to the uterine contractions it may become more and more polypoid, until finally it may appear in the vagina. Even when quite small it may cause marked uterine hemorrhage owing to the irritation of the endometrium which it produces. The overlying endometrium may be remarkably thickened. A large tumor may distend the uterine cavity, giving an appearance which may so closely simulate pregnancy that a correct diagnosis may be impossible even when

the abdomen has been opened. In rare cases the cavity of the uterus may be covered with small tumors. The *subperitoneal* fibroid is centrifugal in growth, so that it becomes subserous and may be pedunculated. *Twisting of the pedicle* may interfere with the blood supply, so that degenerations are most common in this form. In rare cases the tumor may become adherent to the omentum and derive its chief blood supply from that source (parasitic fibroid). The subperitoneal tumors are usually multiple and may attain an enormous size. It is common to find two or all three varieties present in the same uterus.

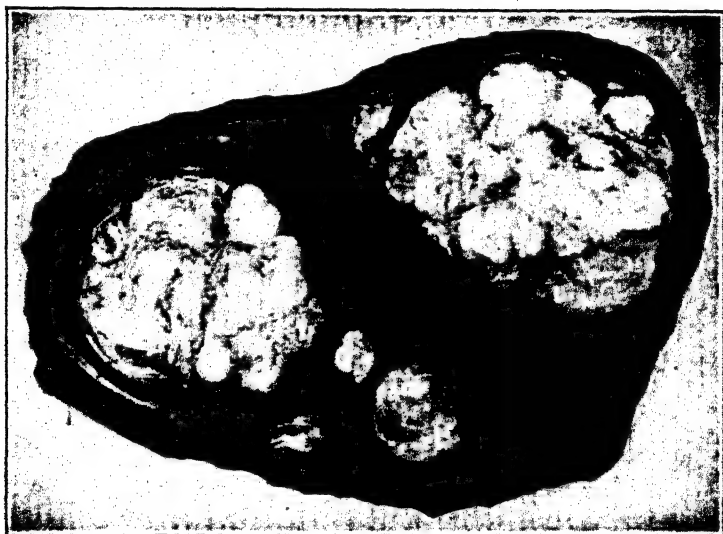


FIG. 361.—Fibromyomata of uterus. The white color is due to the large amount of fibrous tissue.

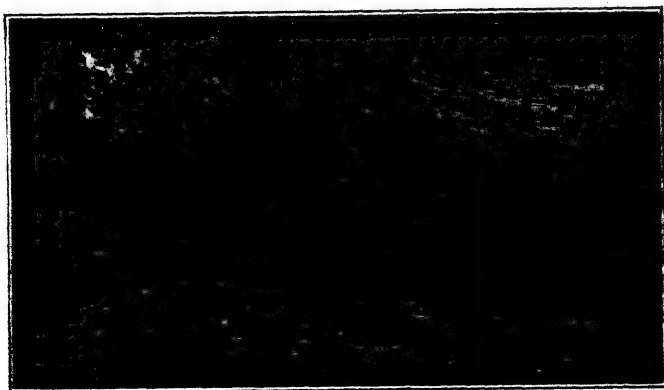


FIG. 362.—Myoma of uterus. The fibers run in interlacing bundles.  $\times 225$ .

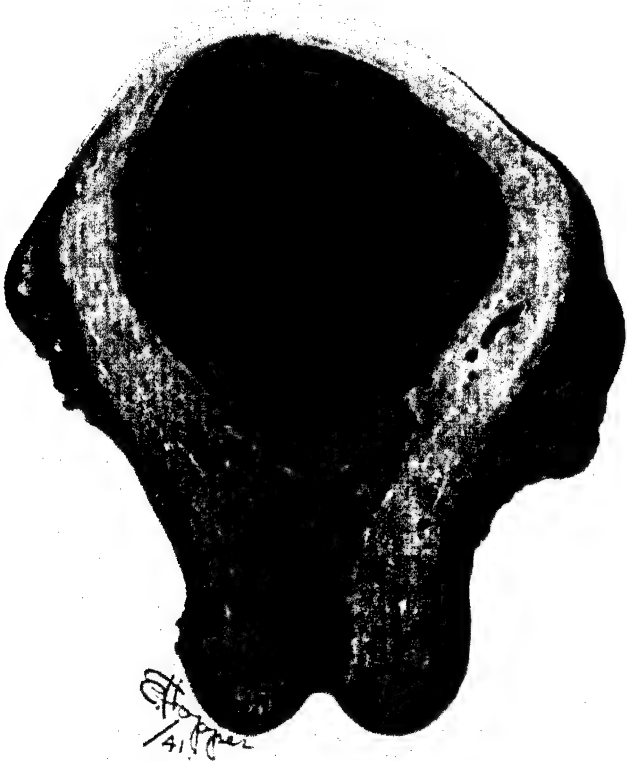
The *microscopic appearance* is a mixture of plain muscle and fibrous tissue in varying proportions. The muscle fibers run in interlacing bundles, some of which are cut longitudinally, some transversely (Fig. 362). The small tumors consist mostly of muscle, but as they grow in size the proportion of fibrous tissue becomes greater, and tumors of long standing may be almost entirely fibrous. The nuclei of the muscle fibers are short, plump, and fusiform, while those of the fibroblasts are longer, slender, and curved.

*Cervical fibroids, i.e.*, tumors originating in the cervix, are not common, although fibroids of the body may invade the cervix. A true cervical fibroid is single. As it grows in size the uterus becomes perched on the summit of the tumor, and if the patient becomes pregnant normal delivery is impossible.

*Degenerations.*—The blood supply of a fibroid is easily interfered with, so that degenerations are common. The subperitoneal form is nourished solely through its pedicle, and it is in this variety that degeneration is most frequent. *Atrophy* may occur after the menopause, due probably to loss of the ovarian stimulus, and a similar result may follow removal of the ovaries. *Hyaline degeneration* is the commonest change, and is due to an insufficient blood supply. The fibrous tissue becomes hyaline, and the muscle fibers tend to disappear. *Cystic degeneration* may follow the hyaline change. The hyaline material becomes liquefied, and cyst-like spaces are formed, but they have no epithelial lining. *Fatty degeneration* is seen in old fibroids. The cut surface is yellow and homogeneous, and the muscle fibers contain fat droplets which can be demonstrated by means of the special stains for fat. *Calcification* may be a sequel to fatty degeneration, and is seen in the subserous fibroids of elderly women. The entire tumor may become converted into a mass of stone, which forms a striking feature in the roentgen-ray picture, but gives rise to no special symptoms. *Red degeneration* is a peculiar change which is commonly regarded as being much commoner in pregnancy. This has not been the case in my own experience. In 38 examples of this condition operated on at the Toronto General Hospital over a period of eight years, 11 (29 per cent) were associated with pregnancy whilst 27 (71 per cent) bore no such relationship. The change is marked by sudden pain and tenderness in the tumor. The latter becomes quite soft and of a bright red color like that of raw beef (Plate XX). The red color is due to a collection of blood in the tissue which becomes hemolyzed and causes diffuse staining of the entire tumor. The condition is probably the result of thrombosis of the veins, so that it may be regarded as a red infarct. The venous obstruction, usually occurring as it does in pregnancy, may be attributed to pressure, contractions of the uterus, or torsion of the tumor. The change is commonest in the interstitial variety. *Sarcomatous degeneration* of a myoma is discussed in connection with Sarcoma of the Uterus.

**Adenomyosis.**—In this condition there is an intermingling of glandular and muscular elements. It is not a true tumor, so that the term adenomyoma, formerly applied to it, is a misnomer. Von Recklinghausen believed that the epithelial elements of the lesion arose from portions of the Wolffian body which had become separated in early fetal life, but Cullen

PLATE XX



Red Degeneration of Uterine Fibroid

showed by means of serial sections that there was direct continuity of epithelium between the lesion and the endometrium. Areas of decidua have been found in the lesion shortly after labor, and even in cases of tubal pregnancy. Although the lesion is sometimes spoken of as a variety of endometriosis, it will be apparent that the relation of the two conditions is merely casual and in no way intimate. Adenomyosis consists of and is derived from endometrium, but in endometriosis the new tissue is more probably of serosal origin.

The *gross appearance* is usually characteristic. The lesion may be limited to the anterior or posterior wall or may form a mantle just outside the mucosa. Although the uterus may be enlarged to two or three times its normal size, and the affected part may be markedly thickened, the normal outline of the organ is usually retained. When the uterus is opened the diagnosis can often be made from the gross appearance. The anterior or posterior wall is diffusely thickened, with a complete absence of the sharp demarcation so characteristic of the ordinary fibroid. The thickened portion of muscle is coarsely striated, and homogeneous translucent areas resembling mucous membrane may be scattered through it. These areas often present a brownish discoloration due to the presence of extravasated menstrual blood. Small cystic spaces filled with chocolate-colored contents may be scattered throughout these mucosal areas. The line of demarcation between the lesion and the normal mucous membrane is always sharp; it extends to, but never into, the endometrium.

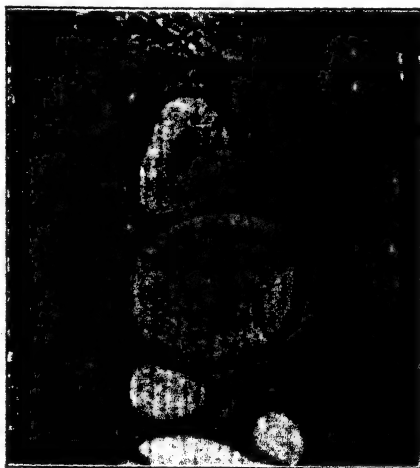


FIG. 363.—Adenomyosis of the uterus. Deep in the wall of the uterus there are dilated endometrial glands surrounded by the cellular stroma of the endometrium.

*Microscopically*, the growth is made up of fibromyomatous tissue, only differing from that of an ordinary fibroid in that it is not encapsulated, together with glandular structures. The latter resemble the normal endometrium, although not so regular in appearance (Fig. 363). "The uterine mucosa is often of normal thickness and looks perfectly normal, but as we approach the underlying diffuse myomatous tissue the mucosa is seen to penetrate it in all directions, sometimes as an individual gland, but often large areas of mucosa are seen extending into the depth. In favorable sections one can follow a prolongation of the mucosa half way through the uterus" (Cullen).

**ENDOMETRIAL STROMATOSIS.**—In endometriosis the dominant element is epithelium. Occasionally the stromal cells of the endometrium assume invasive qualities



under the influence, apparently of hormonal stimulation. Under normal conditions root-like strands of these cells penetrate for a short distance into the muscularis. As the result of abnormal stimulation this invasion may become almost sarcomatoid in its character and form a tumor-like lesion. The stromal cell is in a constant state of flux during the sex life of the individual, and it has a high potentiality for differentiation, so that the mass may resemble a sarcoma (soft) or fibroma (hard) in both gross and microscopic appearance. Undoubtedly in the past this condition has frequently been diagnosed pathologically as sarcoma. A unique feature presented by some of these tumors is the presence on the cut surface of hundreds of worm-like masses occupying the lymphatics and occasionally the veins. In one case with which I am familiar the patient is alive and well four years after removal of the uterus, although long strings composed of masses of interstitial endometrial cells could be pulled out of the vessels of the uterine wall.

**Carcinoma of the Cervix.**—Cancer of the uterus is one of the commonest forms of cancer, and cancer of the cervix is much more common than cancer of the body. The two forms are so different in their behavior that they may be regarded as different diseases. Uterine cancer is much less common in Jewesses than in any other race. Over 90 per cent of cases occur in women who have borne children, and it is noteworthy that the fecundity of patients who eventually develop this form of cancer is above the average. Laceration of the cervix is a frequent antecedent. These facts form the basis for the confident assertion that injury to the cervix is the most important etiological factor. Although this dogma has been accepted for many years, it seems time to call it in question. In no other part of the body does a single laceration, even though followed by infection, act as a carcinogenic agent. It is now known that the epithelium of the cervix is subject to hormonal stimulation, and it is possible that this may be a factor of greater importance than trauma (Hofbauer). The prolonged administration of estrin produces cancer of the cervix in the mouse, an animal in which this form of cancer is unknown as a spontaneous disease (Gardner, *et al.*). It may be noted that cancer of the cervix occurs only in those mice which have shown themselves to be resistant to mammary cancer or in whom this form of cancer has been removed surgically. The highest incidence of female genital cancer occurs at or after the menopause when ovulation has stopped. There is, therefore, no corpus luteum hormone, but the output of estrogen may continue, especially if the ovaries are cystic. Carcinoma of the cervix may occur in women who have been delivered by cesarean section, and in whom there can be no question of laceration of the cervix. In one case with which I am familiar carcinoma developed ten years after delivery by section. It is evident that hormonal imbalance must be considered as a possible agent in the etiology of female genital cancer.

The *gross appearance* may take a papillary form or an infiltrating form. (1) The *papillary variety* forms a large fungating mass, projecting into the cavity of the vagina, and appearing to arise from the lip of the external os. There is little tendency to invasion of the deeper tissues, and as hemorrhage, especially after coitus, is an early symptom, diagnosis may be made fairly early, so that the prognosis is less unfavorable. (2) The *infiltrating variety* (Fig. 364), which is the common one, may give little sign of a tumor

on the surface, but extends deeply in the direction of the internal os, causing enlargement and hardening of the cervix, but unaccompanied by symptoms for a considerable time. In the course of time there is extensive necrosis and sloughing, with destruction of the cervix and the formation of a ragged, badly infected cavity (Fig. 365). Sometimes the cervical canal becomes blocked by the tumor, so that drainage from the uterine cavity is impossible and pus accumulates, often under very high pressure, a condition known as pyometria. A similar state of affairs may be produced by fibrosis and cicatricial contraction of the canal caused by treatment (often cure) of the tumor by radium. When the cervix is painted with Lugol's solution the normal epithelium is colored a deep brown by the iodine (glycogen reaction), while diseased epithelium and cancer is unstained. This is used as a guide for the site of biopsy in early cancer (Schiller test), but unfortunately cervical erosion also remains unstained.



FIG. 364.—Infiltrating carcinoma of the cervix uteri.

The *microscopic appearance* has caused most of the difficulties of classification. Two types of epithelium are found in the cervix. The vaginal

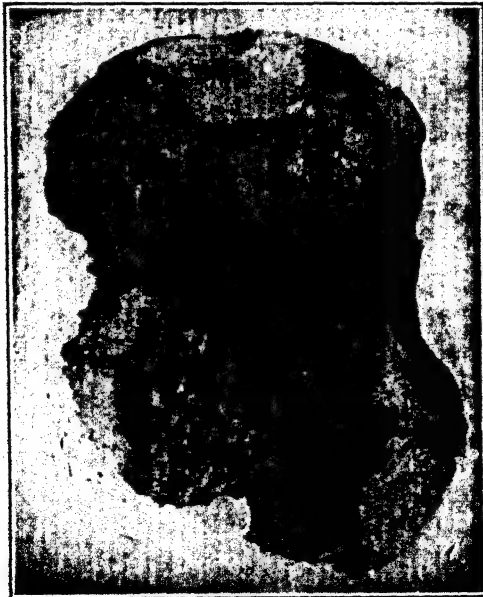


FIG. 365.—Carcinoma of cervix. The cervix is converted into a ragged fungating mass.

portion (portio vaginalis or simply portio) is covered by stratified squamous epithelium of the epidermal type, while the cervical canal is lined by a single layer of columnar epithelium. Corresponding to these two types of epithelium we find two types of tumor, a common epidermoid carcinoma, and a rarer adenocarcinoma which forms less than 4 per cent of the total. But it is not safe to conclude that the former must arise from the portio and the latter from the cervical canal, for squamous epithelium may extend into the canal, and the racemose glands of the portio may be the starting-point of an adenocarcinoma. It seems probable that in the majority of cases the tumor originates at the external os which has been the seat of a cervical erosion with change from a squamous to a columnar type of epithelium and reversion again to a squamous type with gradual development of an epidermoid carcinoma. Columns of cells grow down into the deeper tissues, usually showing numerous mitotic figures.



FIG. 366.—Carcinoma of cervix. The plexiform arrangement of the epidermoid cells is well shown.  $\times 115$ .

Gynecologists have made minute subdivisions according to the type of cell (spinous, transitional, spindle, etc.) in the hope that the radio-sensitivity of the tumors might be determined, seeing that radiation therapy plays such an important part in the treatment of the condition. It seems better to speak merely of the degree of differentiation which the tumor exhibits. The cases of epidermoid carcinoma may be divided into three groups according to their degree of differentiation, and these groups show a corresponding variation in degree of radiosensitivity (Healy and Cutler). Group 1 (20 per cent) is the *adult type*, made up of highly differentiated cells with a tendency to cornification and the formation of pearls. It is radio-resistant. Group 2 (60 per cent) is the *plexiform type* in which the cells have lost most of their squamous character, show a plexiform arrange-

ment, a tendency to infiltration, and a moderate degree of anaplasia (Fig. 366). The tumor is more radio-sensitive. Group 3 (20 per cent) is the *anaplastic type* in which the cells have lost all squamous characters, are completely undifferentiated and diffusely invasive. They are highly radio-sensitive. When the results of radiation therapy are analyzed the curious position is revealed that the best results (permanent cure) are obtained with the most malignant tumors, *i.e.*, those of Group 3. The reverse is the case when the growths are removed surgically. The rather uncommon adenocarcinoma seems to be less invasive than the epidermoid form, so that the operative results are more favorable, but it is less radio-sensitive.

*Intraepithelial carcinoma*, also known as preinvasive carcinoma and carcinoma *in situ*, is one of the most contentious and most important aspects of cervical cancer. As the name implies, the basal epithelial layers take on characteristics suggestive of malignancy, both as regards the appearance of the nucleus and the basophilic staining of the cytoplasm due to increase of ribonucleic acid and lack of the glycogen normally present in the epithelium in this region (Fig. 157, page 271). The picture is one of cellular unrest, and it is liable to cause similar unrest in the mind of the pathologist. Some of these lesions undoubtedly go on to invasive carcinoma, while others do not. At the present time it is not possible to say if in any given case the process is reversible or irreversible. This much, however, is certain. These lesions are far more frequent than is the incidence of invasive carcinoma. From this it would appear that the majority of cases of so-called intraepithelial carcinoma do not develop into true cancer.

The method of diagnosing uterine cancer by examining the cells of a vaginal smear, first suggested by Papanicolaou in 1928, has become a standard procedure which is of particular value in early cases. The material is aspirated, blown on to a slide, fixed before being allowed to dry, and stained. A positive result indicates that a confirmatory biopsy should be performed. In cervical cancer abnormal cells are found in the smear showing great variety of form and size, atypical structure of their nuclei, and vacuolization of the cytoplasm.

**SPREAD.**—Spread may occur by permeation, by the lymph vessels, or by the blood stream. *Permeation* may carry the tumor cells outward to the parametrium, forward to the bladder, backward to the rectum, and downward to the vagina. It is very seldom that the tumor spreads so as to invade the body of the uterus, although the entire cervix may be involved. Obstruction of the ureters is common, causing an ascending infection which may prove fatal. *Lymphatic spread* leads to involvement of the iliac, hypogastric and sacral groups of lymph nodes. The tumor generally metastasizes late; only about 50 per cent of autopsy cases show gross metastases, and in radical hysterectomies lymph-node involvement averages about 30 per cent. Cullen found malignant nodes in only 2 per cent of cases where the disease was still confined to the uterus. *Blood spread* is not common and is only found in advanced cases, in accordance with the rule that epidermoid carcinoma does not tend to invade the blood vessels.

**Carcinoma of the Body of the Uterus.**—Cancer of the body of the uterus is much less common than cancer of the cervix, constituting only 10 per cent of the cases of uterine carcinoma. It occurs later in life, usually after the menopause, so that irregular bleeding is more likely to cause alarm. It is much less infiltrative than cervical carcinoma. For these reasons the prognosis is more favorable. Childbearing is not an etiological factor, for it is even more common in nulliparæ than multiparæ.

The tumor usually begins in the endometrium of the fundus and spreads superficially so that a large surface may be involved (Fig. 367). It assumes



Fig. 367.—Carcinoma of the body of the uterus. The uterus is bicornuate, and the carcinoma fills the cavity of both horns.

the papillary rather than the infiltrating form, and may constitute a mass which occupies the greater part of the uterine cavity, and causes a moderate degree of enlargement of the organ. Involvement of the cervix is very rare. Invasion of the muscular wall occurs in time, so that care must be exercised in performing a diagnostic curettage to avoid perforating the uterus, but there is never the early involvement of the parametrium which is so characteristic of cancer of the cervix. Curettage gives definite chunks of cancer tissue; if the scrapings are scanty, soft and pink, they are almost certain not to be malignant.

*Microscopically*, the picture is usually that of a typical adenocarcinoma with irregular malignant tubules invading the underlying muscle. Sometimes the structure is more anaplastic with little glandular formation.

Diagnosis from fragments of scrapings is not always easy unless some muscle is included, for the new-formed glands may resemble those of endometrial hyperplasia. Attention must be paid to irregularity of staining, mitosis and evidence of invasion. Generally speaking the cytological rather than the histological features are those which count. When the pathologist is in doubt, it is generally not cancer. Histological grading of biopsy material is singularly disappointing and of little prognostic value, as different blocks may show widely varying pictures. Occasionally the carcinoma may be epidermoid in type. In rare cases the tumor may take the form of adeno-acanthoma, *i.e.*, a combination of glandular and epidermoid carcinoma.

**SPREAD.**—Spread takes place through the muscular wall, with eventual perforation. Fragments of tumor may be carried through the Fallopian tubes and infect the ovaries, so that the ovaries must always be removed together with the uterus. Lymph spread to the paravertebral glands and blood spread to lungs and liver occur in the later stages.

**SARCOMA.**—Sarcoma of the uterus is an uncommon tumor. It usually occurs as a malignant change in a myoma, so that it may be called a myosarcoma or malignant myoma. Occasionally it may arise from the normal uterine wall. The *gross appearance* is characteristic, for the whorled or striated appearance of the fibroid is lost, the cut surface is homogeneous and brain-like, and the tumor is soft and may be of a yellowish color. Cyst formation and hemorrhage are frequent. *Microscopically* the tumor is composed of large fusiform cells, in many of which the nuclei are remarkably large and may show numerous mitoses. It is almost impossible to be certain if these cells are derived from plain muscle or from fibroblasts.

**ENDOMETRIAL SARCOMA** is usually circumscribed but may be diffuse. It originates in the fundus, and often forms a polypoid bulky mass in which necrosis may occur as well as cystic areas of hemorrhage. Microscopically it consists of a mixture of fusiform and large spherical cells. The degree of mitosis parallels the clinical malignancy of the tumor. Invasion of the uterine muscle occurs, and spreads to peritoneum, regional lymph nodes and distant organs.

**EMBRYONAL TUMORS.**—These are very rare tumors containing a variety of tissues of mesodermal origin, of which striated muscle is the chief. The general structure is sarcomatous and they are usually called sarcomas or rhabdomyomas. The best-defined variety is the so-called *grape-like sarcoma* of the cervix or vagina, which usually occurs in young children, and projects into the vagina in polypoid masses that may become so edematous as to resemble a bunch of grapes. Most of the cells are round or fusiform, but striated muscle is usually present. The tumor is very malignant, and spreads both locally and by the blood stream.

**Chorionepithelioma.**—This highly malignant tumor, which arises from fetal and not maternal tissue, usually follows an abortion, sometimes is the result of a full-term pregnancy, and in rare cases has been found in the ovary and in the testicle. In about 30 per cent of the cases it is preceded by a hydatidiform mole, a benign epithelial tumor of the chorionic villi which will be described in connection with the pathology of the placenta. It is said that about 15 per cent of hydatidiform moles may show this malignant change, but it is impossible to get accurate figures, and this proportion is probably much too high. Both chorionepithelioma and hydatidiform mole are often associated with an unusually large corpus luteum or bilateral lutein cysts. The connection is not certain, but it is

probable that they are a result rather than a cause of the uterine condition. The tumor may develop very soon after pregnancy, or there may be an interval of months or years. The Aschheim-Zondek test for pregnancy is markedly positive. (See Hydatidiform Mole, p. 647.)

The tumor commences at the placental site, usually in the fundus of the uterus. It forms a soft, red, highly hemorrhagic mass which projects into the cavity and at the same time invades the muscular wall. Secondary growths may be formed in the lower part of the uterus and in the vaginal wall; in the latter position the progress of the disease can be watched and the effect of treatment noted. Later the tumor appears on the outer surface of the uterus.



FIG. 368.—Chorionepithelioma consisting of clear Langhans' cells and dark syncytial masses.  $\times 350$ .

*Microscopically* the chorionepithelioma is an exaggeration of the condition normally found in pregnancy. The fetal part of the placenta consists of the chorionic villi, and the essential part of the villus is the trophoblast, the function of which is to invade the maternal blood sinuses. The trophoblast presents two types of epithelium, an inner layer of clear cubical cells with large pale nuclei known as Langhans' cells, and an outer layer of large dark multinucleated masses of cytoplasm known as the syncytial cells. The chorionepithelioma consists mainly of clear Langhans' cells with a varying proportion of dark syncytial masses lying in large pools of blood (Fig. 368). The normal relationship of the two types of cell is lost, for the exuberant Langhans' cells have burst through the outer syncytial layer. There is no stroma nor blood vessels, as the tumor is nourished by the blood in the vessels it invades.

**SPREAD.**—Spread is almost entirely by the blood stream, owing to the fundamental tendency of the trophoblastic cells to invade blood vessels. Distant metastases in the lungs, etc., may be set up at an extraordinarily early date after an abortion. The secondary tumors are as hemorrhagic as the primary growth and show the same microscopic structure. Second-

ary nodules may appear in the vaginal wall. These are not implantations, for the tumor cells lie within vessels.

Not all cases run the rapidly fatal course of the ordinary chorionepithelioma. Some cases make a complete recovery when the primary growth is removed, and spontaneous disappearance of the metastatic growths has even been reported after this operation; this disappearance may be watched in the case of secondary nodules in the vagina. There is one small group of tumors (about 5 per cent) in which the structure is comparatively benign with a corresponding absence of blood vessel invasion and formation of metastases. The growth consists of syncytial cells only, with no admixture of Langhans' cells. The tumor is therefore known as a *syncytioma*.



FIG. 369. Hydatidiform mole.

## PATHOLOGY OF THE PLACENTA

**Hydatidiform Mole.**—The word mole means mass. A hydatidiform mole is a not uncommon condition (1 in 2500 or 3000 cases) in which the placenta is converted into a mass of grape-like bodies resembling hydatid cysts (Fig. 369). The cysts, which may be as small as a pin's head or as large as a grape, represent a cystic degeneration of the connective tissue of the chorionic villi, but the fundamental condition is a proliferation of the epithelium of the villus, both Langhans' cells and syncytium, so that there are several layers of the former and the syncytial cells are unduly prominent. It may therefore be regarded as an innocent epithelial tumor, of which the malignant variety is the chorionepithelioma. When the change occurs early the fetus and placenta disappear, being replaced by a mass or mole composed of cyst-like bodies. When the change takes place later there may be a small atrophic fetus and remnants of placenta. Sometimes the change may be microscopic; these cases are much commoner than the fully developed ones (Fig. 370). The formation of a mole leads to abortion



and may cause severe hemorrhage. We have already seen that at least part of the hormone which appears in the urine during pregnancy and gives the Aschheim-Zondek test for that condition is produced by the placenta. With the termination of pregnancy and complete removal of the placenta the test at once becomes negative. If portions of the placenta are retained or if hydatidiform mole or chorionepithelioma develop, the hormone continues to be produced and the test remains positive. When an innocent mole is removed the test becomes negative. If it remains positive it indicates that chorionepithelioma has developed. As long as active chorionic epithelium remains in the uterus, the test remains positive.

**Toxemias of Pregnancy.**—This serious complication of the latter part of pregnancy is divided into preëclampsia and eclampsia. The former, which is much the commoner, consists of the edema and albuminuria with the significant addition of hypertension. If convulsions develop the condition becomes eclampsia.

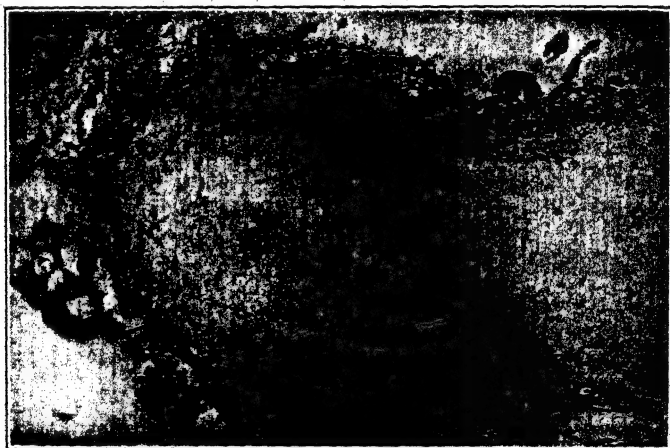


FIG. 370.—Hydatidiform degeneration of a chorionic villus. There is mucoid degeneration of the connective tissue and proliferation of the epithelium covering the villus.  $\times 25$ .

The chief lesions are in the kidney, liver and placenta. Both kidneys are swollen, and the glomeruli present a solid ischemic appearance (glomerulosclerosis) which has been described on page 565. Symmetrical necrosis of the renal cortex is a very rare complication (page 594). The liver lesions, the characteristic patches of hemorrhagic necrosis, are described on page 501. They are not nearly so constant nor fundamental as the renal lesions. In the placenta the characteristic change is a premature ageing as evidenced by syncytial degeneration, together with more numerous infarcts than are found in normal pregnancy. The convulsions appear to be due to hypertensive cerebral edema.

Generalized edema of varying degree is found in over 60 per cent of normal pregnant women. This is not due to any of the usual causes of edema, and a hormonal etiology is suspected. The hypertension of toxemia usually disappears after delivery. On the other hand mild toxemia

may be followed by permanent hypertension, so that the toxemia of pregnancy is one of the causes of permanent hypertension in the female.

Eclampsia has been called "the disease of theories." At the present time it is believed that the placenta may produce a pressor substance which acts directly on the arterioles, or a toxic substance acting on the glomeruli causing renal ischemia and thus renal hypertension. One thing is certain and that is that vasoconstriction does occur, for it can be observed with the ophthalmoscope in the retinal arteries. If the vasoconstriction and hypertension persist for more than a few weeks, permanent vascular changes may develop and the hypertension becomes irreversible. A full discussion of the problem will be found in the monograph by Dexter and Weiss.

**RETAINED PLACENTA.**—After an abortion or a full-term pregnancy portions of placenta may be retained in the uterus. The villi may remain alive for many months and may appear perfectly normal when removed by the curette. The pathologist must therefore be cautious about expressing an opinion as to how long a time may have elapsed after the last pregnancy, especially in medico-legal cases. In the course of time the villi undergo hyaline degeneration. The stage to which pregnancy has advanced may be roughly estimated by remembering that before mid-term the villi are relatively avascular and the Langhans' cells are prominent, while after that time the villi become vascular and are covered only by syncytial cells, the Langhans' cells disappearing (Fig. 371).

**UTERO-PLACENTAL APOPLEXY.**—This is a complication (possibly a cause) of premature separation of the normally implanted placenta. There may be most extensive hemorrhagic infiltration of the decidua and the uterine wall; (for an excellent colored plate see Williams' book). In one case which I examined the muscle fibres in places seemed to be floating in pools of blood. In this case the decidual vessels showed acute inflammatory changes which may have been the primary cause both of the uterine apoplexy and the separation of the placenta.

**PLACENTAL INFARCTS.**—These are localized areas in the placenta, which may be red when they consist chiefly of coagulated blood, or pale yellow when the blood is decolorized and there is much necrosis of tissue. They constitute one of the commonest abnormalities of the placenta. Minute infarcts are indeed present in every placenta. Sometimes large wedge-shaped segments are involved. The accepted



FIG. 371.—Placenta at full term. Above are vascularized villi with syncytial cells; below is decidua.  $\times 225$ .



FIG. 372.—Normal placenta.  $\times 280$ .



FIG. 373.—Placenta in erythroblastosis.  
 $\times 280$ .



FIG. 374.—Syphilitic placenta showing thickened and relatively avascular villi.  $\times 175$ .

basis for the condition is an endarteritis of the vessels in the chorionic villi causing necrosis of the villi followed by coagulation of the blood between the villi, and matting together of the latter by fibrin. In many cases, however, no endarteritis can be found, so that another explanation must be sought. After the seventh month the Langhans' cells disappear and the syncytium may also atrophy in patches, as a result of which fibrin becomes deposited on the rough surface. The layer of fibrin cuts off the villi from their blood supply in the maternal sinuses so that they undergo necrosis. In this case the process is an ischemic necrosis but not an infarction. *Calcification* is not uncommon in these necrotic areas.

**ERYTHROBLASTOSIS FETALIS.**—The placenta is very large and edematous, particularly in the hydropic form of the disease. Microscopically the villi are swollen, the Langhans' cells which normally disappear about the middle of pregnancy still persist, and the capillaries contain numerous erythroblasts. These changes make a diagnosis possible even when the fetus has become completely macerated (Figs. 372 and 373).

**SYPHILIS.**—When the fetus is syphilitic the placenta may be normal, but often it is thick and pale. The pallor is due to avascularity. The normal villi are very vascular, but in syphilis they may become markedly avascular owing to endarteritis, and considerably thickened (Fig. 374). In judging of avascularity it must be borne in mind that it is only in the second half of pregnancy that the villi are vascular for in the earlier months they contain very few vessels.

**TUBERCULOSIS.**—Tuberculosis is rare. Miliary tubercles may occur, or larger caseous masses.

## THE FALLOPIAN TUBES

Although the only function of the Fallopian tubes is to carry the ovum from the ovary to the uterus, the mucous membrane shares in the general cyclic changes of menstruation. There are two types of epithelial cells, ciliated and non-ciliated. In the advanced secretory phase the ciliated cells become much lower, and the non-ciliated cells project between them, with bulbous herniation into the lumen of the tube. During menstruation both sets of cells become low. This lowness is greatly accentuated during pregnancy, when they become almost flat. After menstruation the cells regain their normal height in three or four days.

The Fallopian tubes are peculiarly liable to inflammation. Tumors and other lesions are of little importance. The tubes may be infected from either end as well as from the blood stream. The narrow uterine opening, which is so easily closed by swelling of the wall, and the very numerous folds of mucous membrane tend to make an infection of long duration. Salpingitis or inflammation of the tubes is due to infection with the gonococcus in about 80 per cent of cases. Pyogenic cocci, especially streptococci, are responsible in about 15 per cent, and the tubercle bacillus in the remaining 5 per cent. Streptococci can be grown from the tubes many months or years after the primary infection, but the gonococcus may die out in the course of a few months.

## GONORRHEA

Before describing gonorrheal salpingitis it is convenient to make a brief survey of gonorrheal infection of the female genital tract. The primary in-

fection is usually in the urethra, occasionally in the cervical mucosa. Both of these are lined by a layer of epithelium which is readily penetrated by the gonococcus. The cornified squamous epithelium of the vulva and vagina is seldom infected except in children, in which it is soft and delicate. It is evident that when smears are made they must *not* be taken from the vagina, but from the cervix and urethra. The infection in the urethra usually gives rise to little or no clinical disturbance, so that it is difficult to determine with accuracy the date of infection. *Bartholin's glands*, situated on either side of the posterior commissure of the vaginal entrance, may become infected from the urethra, with the formation of an acute abscess. Acute bartholinitis is almost always gonococcal in nature. The *cervix* is involved primarily or secondarily in most cases of gonorrhea, but as it is a very insensitive organ there are often no symptoms. It is in the mucous membrane of the cervical canal that the infection becomes chronic, for the branching racemose glands of the endocervix form an ideal lurking place for the gonococcus, from which it may issue periodically to infect other parts of the genital tract. Laceration after childbirth and gonorrhea account for nearly all cases of endocervicitis and cervicitis. The *endometrium of the body* of the uterus is seldom seriously infected. When first invaded by the gonococcus there are no doubt suppurative lesions of the superficial layers, but these are swept away at the next menstrual period, and it is seldom that chronic infection of a serious nature occurs. When the gonococcus reaches the *tubes* it finds as favorable a habitat as the endocervix, and the most serious results of gonorrhea in the female occur in the tubes. Before considering gonococcal salpingitis a few words may be devoted to gonorrhea in children.

*Gonorrheal vulvovaginitis* is practically confined to children, because in them the vaginal epithelium is not yet cornified and is readily penetrated by the gonococcus. The disease is extraordinarily contagious, and may sweep like a fire through a school or a children's hospital. The infection is spread by towels, sponges, etc., but often it is difficult to determine the exact means of spread. Once the infection is established it is very resistant to treatment. Anyone who has had practical experience with this disease in a hospital will be struck by the marked discrepancy between the laboratory findings and the clinical evidence of the disease. When routine vaginal smears are made in a hospital, Gram-negative intracellular diplococci are not infrequently found in children who show no symptoms of any kind. It is possible that in many cases the organisms seen are not gonococci but *Micrococcus catarrhalis*, which is morphologically indistinguishable from the gonococcus and is known to be capable of causing vaginitis in children. The distinction can readily be made by culture.

**Gonorrheal Salpingitis.**—Infection of the tubes may occur early in the disease, but there is often a considerable interval. During this time the gonococcus is lurking in the racemose glands of the cervix, from which retreat it may invade the tubes at any time. The infection is practically always bilateral. The effect depends entirely on the intensity of the inflammation. In mild cases it has the character of a catarrh, while in more severe form it becomes purulent. There is a tendency for both ends of the tubes to become closed even though the inflammation be mild. The outer end may be closed by the inflamed fimbriae becoming withdrawn into the

ostium of the tube and adhering together, or by becoming adherent to the ovary. The inner end, which normally is less than 1 mm. in diameter, is easily closed by inflammatory swelling of the mucosa. The tube is now a closed cavity, and if a fluid exudate is poured out as the result of inflammation the tube will be distended. The distention is most marked at the distal end, and the tube becomes curved into a form like a retort. When the exudate is more or less serous (catarrhal salpingitis) the result is hydro-salpinx; when it is purulent a pyosalpinx is formed.

In *hydrosalpinx* the distention of the tube may be great, but the wall is thin and translucent, for there is no pronounced inflammatory thickening. The mucosa is atrophic, and the contents clear and watery, though rich in albumin. In *pyosalpinx* the wall is much thickened and the distended tube is filled with thick pus. The wall is infiltrated with inflammatory cells, polymorphonuclears in the early stages and lymphocytes and plasma cells later. In the tube as in the cervix the plasma cell is the characteristic cell of chronic inflammation. It is seldom that the gonococcus can be found in the pus except in recent cases, but secondary infection with *Bacillus coli* is rather frequent. If the inner end of the tube is not closed, there is no distention and the condition is called a *pus tube*. In *tubo-ovarian abscess* the inflamed fimbriæ adhere to the ovary, and infection of the ruptured Graafian follicle is a natural result. The gonococci flourish in the hemorrhagic tissue of the corpus luteum, and an abscess is formed which distends the ovary and communicates with the pyosalpinx by a narrow opening. The tube and ovary together form one large retort-shaped bag of pus. Very dense pelvic adhesions around the tubes and ovaries are a common result. *Salpingitis isthmica nodosa* is a peculiar condition in which nodules are formed at the inner end (isthmus) of the tube. As the result of persistent inflammation areas of mucosa are included in the deeper layers and may become separated from the lumen so as to give an adenomatous appearance. The condition is nearly always gonorrheal in origin, but is occasionally found in tuberculous salpingitis. It causes closure of the tube. From what has been said it is easy to see the relation which gonorrhea bears to sterility and chronic invalidism in women.

## TUBERCULOSIS OF THE FALLOPIAN TUBES

Tuberculous salpingitis resembles gonorrheal salpingitis in some respects, but differs from it in others. The mode of infection is quite different, being nearly always hematogenous from some distant focus, rarely from the peritoneal cavity in abdominal tuberculosis, and never from the lower genital tract. It is almost always bilateral, like the gonorrheal form, and is accompanied by adhesions which are even firmer and may make removal of the tubes quite impossible.

The tubes are thickened, and there may be tubercles on the serous surface. The ostium usually remains open, in contrast to what occurs in gonorrheal salpingitis. Occasionally it may be closed, so that a *tuberculous pyosalpinx* develops, which may be indistinguishable from the gonorrheal form. The contents are characteristically thick and in old cases may be-

come putty-like. Caseation, tubercle formation, epithelioid cells, and giant cells in the mucosa and other layers form a characteristic microscopic picture (Fig. 375).

Infection may spread from the tubes to the peritoneum. Persistently recurring tuberculous peritonitis in the female sometimes clears up only when the tubes are removed.

### TUBAL PREGNANCY



FIG. 375.—Tuberculous salpingitis.  
× 125.

The ovum takes nearly a week to pass along the Fallopian tube from the ovary to the uterus, and it is during its passage down the tube that it becomes fertilized. If the impregnated ovum is arrested in the tube it may develop there and form a tubal pregnancy. The arrest is usually due to chronic salpingitis, as a result of which the folds of the tube are thickened and deep glandular pockets are formed in which the ovum is entrapped. This explains the rarity of the condition in nulliparæ, and the fact that there is often a long interval of sterility between the last pregnancy and the occurrence of the tubal pregnancy. The ovum is usually arrested in the outer end of the tube, the ostium becoming closed by the end of the second month. When development takes place in the inner part of the tube the ostium remains open.

There may be slight decidual formation in the tube, but it is never marked. The normal uterine decidua offers a good deal of resistance to invasion by the chorionic villi, and as this resistance is absent in the tube the villi are able to penetrate deeply into its wall. The ovum may burrow into the muscle, becoming separated from the lumen by the mucosa and some of the muscular layer. It now lies in a cavity in the wall of the tube, a cavity bounded on both sides by muscle and completely separated from the lumen which may be much narrowed (Fig. 376). A well-marked decidua is formed in the empty uterus, and this is sometimes expelled as a decidual cast. The uterus becomes enlarged owing to muscular hypertrophy caused by hormonal stimulation. Uterine scrapings show decidual cells but no chorionic villi, a dissociation only found in extra-uterine pregnancy.

The pregnancy is usually terminated before or at the end of the second month, although in rare cases it may go on much longer or even to full term. *Tubal abortion* is the common method of termination. Hemorrhage



occurs into the gestation sac, destroying the embryo, distending the tube with blood so that it forms a *hematosalpinx*, and converting the products of conception into a *tubal mole* (*mole*, mass). The mole consists of firm blood clot in which chorionic villi are found under the microscope, but no fetal parts. Blood escapes through the ostium if it is still open, the mole be-



FIG. 376.—Tubal pregnancy. A large cavity in the wall of the distended tube is occupied by (1) chorionic villi; (2) dark blood clot; and (3) the gestation sac, which is the crescentic structure to the right with the body cavity in its lowest part. The lumen of the tube is seen to the left.  $\times 7$ .

comes detached, and may be extruded by the muscular contractions of the tube into the abdominal cavity. In very rare cases a mole formed in the isthmus of the tube has escaped into the uterus. At the time of the abortion there is a flow of blood from the uterus. This really comes from the uterus,



not from the tube, being due to breaking down and discharge of the decidua. *Tubal rupture* occurs in about 25 per cent of cases. The wall of the tube is perforated by the trophoblast of the chorionic villi, bleeding occurs into the abdominal cavity, and the patient may die of internal hemorrhage. In rare cases the fetus may be slowly extruded through the ostium without severe hemorrhage. It may then be converted into a *lithopedion*, a mummified mass in which calcium salts are deposited.

### TUBAL CYSTS

Small *subserous cysts* about the size of a pin's head are common and are readily mistaken for miliary tubercles. They are probably formed from the peritoneum as the result of mild inflammation. *Cysts of the hydatids of Morgagni* are also fairly common. The cyst is about the size of a pea, filled with clear fluid, and attached by a slender stalk to one of the fimbriæ of the tube.

### TUMORS OF THE FALLOPIAN TUBES

Carcinoma of the Fallopian tube is the rarest of the primary cancers of the female reproductive tract, but the most malignant. The lumen is distended by adenocarcinoma. The clinical features are vaginal bleeding, a pelvic mass, lower abdominal pain and adenocarcinoma masses of cells in the vaginal smears.

### THE OVARIES

**DESCRIPTIVE OUTLINE.**—It is important to realize the gross appearance of the ovary in health, otherwise the surgeon may remove a normal organ. Each ovary is an elongated flattened body, the surface of which presents bosses (follicles, corpora lutea) separated by fissures and scars. The length is 2.5 to 5 cm., the width 1.5 to 3 cm., and the thickness 0.5 to 1.5 cm. The weight is 5 to 7 grams. Most of the surface is covered by glistening peritoneal mesothelium, but this changes to a lusterless surface (germinal epithelium) along the *white line* which marks the hilum of the ovary, i.e., the site of attachment of the mesovarium. The cortical zone contains ripening Graafian follicles forming cysts of varying size, sometimes up to 1.5 cm. in diameter. Still larger, and often mistaken by the ignorant for a pathological lesion, is the corpus luteum. In some cases it may occupy one-third of the ovary. The center is filled with fresh blood, and the wall is of a characteristic bright yellow color and an equally characteristic wavy convoluted outline. After the menopause the ovaries are small, hard and fibrous, often deeply fissured and scarred.

The essential element of the ovary is the germinal epithelium which is continuous embryologically with the endometrium and the lining of the Fallopian tubes. At birth the germinal epithelium covers the surface of the organ, but during development all the Graafian follicles are derived from this tissue. The maturation of these follicles and the fate of the follicles which do not mature are considered in connection with the subject of cysts of the ovary. The ovarian stroma is peculiar in that it is not fibrous but entirely cellular, the cells being for the most part fusiform, though many of them are round. This cellularity must not be mistaken for evidence of inflammation or tumor formation.

## INFLAMMATION OF THE OVARIES

Inflammation of the ovary is usually the result of infection of the ovary from the Fallopian tube in the course of puerperal sepsis or gonorrhea. It is occasionally infected from the blood stream in infectious fevers.

Acute diffuse inflammation (oöphoritis) is generally caused by puerperal sepsis. The ovary is covered by the tough fibrous tunica albuginea which lies under the germinal epithelium and forms a formidable barrier to invading microorganisms. In puerperal sepsis there is pelvic peritonitis, so that the ovary may be bathed in pus containing virulent streptococci which overcome the barrier of the tunica albuginea and may cause an acute inflammation. Both ovaries are enlarged, congested, and contain numerous small abscesses. In general septicemia acute oöphoritis is a rare complication due to blood infection. The inflammation which may accompany mumps is non-suppurative.

*Ovarian abscess* is usually due to invasion of the ruptured Graafian follicle by the gonococcus. This may be rendered easy by fusion of the fimbriae of the tube with the ovary. It sometimes occurs in puerperal sepsis. The wall of the abscess is at first formed by the yellow wall of the corpus luteum, but in time the abscess involves the entire ovary which becomes converted into a bag of pus. This may fuse and communicate with the tubal abscess so as to form a tubo-ovarian abscess.

## CYSTS OF THE OVARY

Some of the cysts of the ovary are in the nature of retention cysts. Others are true epithelial tumors which assume a cystic form, and these will be considered in connection with tumors of the ovary.

During the course of the menstrual cycle a number of follicles approach maturity, the germinal epithelium proliferating to form several layers of *granulosa cells*. These follicles may develop along one of two lines. (1) The ripe follicle at mid-term of the cycle approaches the surface, discharges the ovum, and becomes converted into the *corpus luteum*, the granulosa cells proliferating and acquiring a high lipid content which gives the new structure its yellow or lutein color. The corpus luteum is an organ of internal secretion which acts on the endometrium and the other developing follicles, but after menstruation it undergoes rapid hyaline degeneration, and becomes changed into a structureless white mass, the *corpus albicans*. If pregnancy supervenes the corpus luteum does not degenerate, and continues to increase in size. (2) Under the influence of the lutein hormone the other maturing follicles undergo retrogression or *atresia*. It is from these atretic follicles, which may be regarded as examples of arrested development and are still lined by granulosa cells, that the majority of retention cysts probably arise. The stromal cells in contact with the developing follicle are known as *theca cells*. During atresia they become enlarged, acquire a lipid content, and assume an epithelioid character, being known as *theca-lutein cells*.

**Follicular Cysts.**—These very common lesions of the ovary are retention cysts of atretic follicles. The cysts are small, seldom more than 3 cm. in diameter, multiple, and sometimes are so numerous as to involve the entire ovary, producing some enlargement. The cyst is lined by epithelium which is cuboidal in the small cysts but flattened in the larger ones. There is

generally an associated fibrosis of the ovary, hence the old name of sclerocystic disease of the ovary. One cyst may grow at the expense of the others which it absorbs, and may reach the size of a plum or even a tangerine orange, the remaining cysts disappearing. The contents are clear and watery, and there is no trace of an epithelial lining in these larger cysts. In the ovaries of infants and even in the new-born there may be large numbers of small follicular cysts. These must be due to some abnormal hormonal stimuli (maternal); possibly some similar mechanism may be responsible for follicular cysts in the adult.

**Lutein Cysts.**—These cysts may represent degeneration of the corpus luteum formed after ovulation, or they may be *theca-lutein cysts* formed from atretic follicles lined by luteinized cells. The distinction between the two types is often difficult. Hemorrhage is frequent into both varieties. The hemorrhage may be severe, extend into the interstitial tissue, and form a *hematoma*. This may rupture into the abdominal cavity causing severe internal hemorrhage with symptoms simulating ruptured tubal pregnancy or some other abdominal catastrophe. The hemorrhage may prove fatal unless the ovary is at once removed.

**Endometrial Cysts (Chocolate-colored Cysts).**—These are examples of endometriosis, *i.e.*, ectopic development of endometrium-like tissue. They are small, often multiple, and of a dark reddish-brown color (chocolate) due to the presence of old blood. They are situated on the surface of the ovary and may show evidence of previous perforation. The cysts represent endometrial glands into which menstrual hemorrhage has occurred. The condition is probably an example of metaplasia due to hormonal stimulation of a tissue which is related developmentally to the endometrium rather than a result of endometrial implants.

## TUMORS OF THE OVARY

Tumors of the ovary may be *cystic* or *solid*. The former are very much more common, and are known as cystadenomas. They are for the most part innocent, though they may become malignant; the solid epithelial tumors, on the other hand, are practically all malignant. The cystadenomas may be divided into two main groups, the pseudomucinous and the serous. These differ not only in their contents, but also in structure and behavior. There is a rare third group of tumors associated as a rule with sexual endocrine dysfunction for which there is no very appropriate name, but which may be called the *special group*.

**Pseudomucinous Cystadenoma.**—This is a common tumor, usually unilateral, and may reach very large dimensions. It is always multilocular, owing to the formation of daughter cysts from projecting buds of the lining epithelium. The daughter cysts vary greatly in size, a few may grow to a large size at the expense of the others, the intervening walls becoming broken down. The *contents* are very thick, mucoid, and stringy (Fig. 377). Though resembling mucin the material does not give the characteristic mucin reaction with acetic acid and is therefore known as pseudomucin. The fluid may be turbid and tinged with blood, or it may be shimmering with crystals of cholesterol. The cyst develops a well-marked

pedicle, and this may become twisted, producing intense congestion of the wall, hemorrhage into the cavities, and a clinical picture of acute strangulation.

The *microscopic picture* is characteristic. The cysts are lined by a layer of very tall columnar epithelial cells with extremely clear cytoplasm (due to the mucinous content) and nuclei situated at the base of the cells (Fig. 378). There may be small papillary projections from the wall of the cyst.

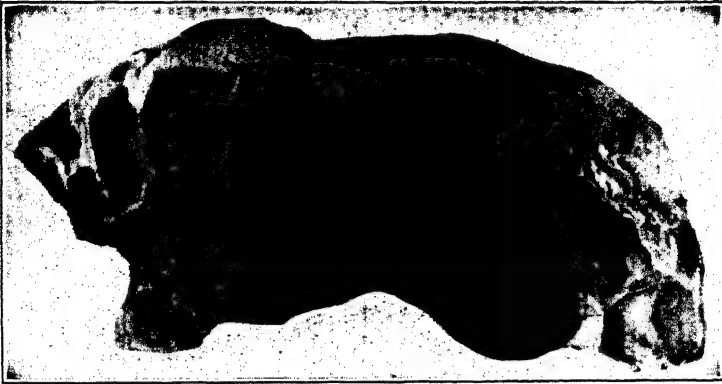


FIG. 377.—Pseudomucinous cystadenoma of the ovary. The cysts are filled with thick mucinous material which has been coagulated by the fixative.

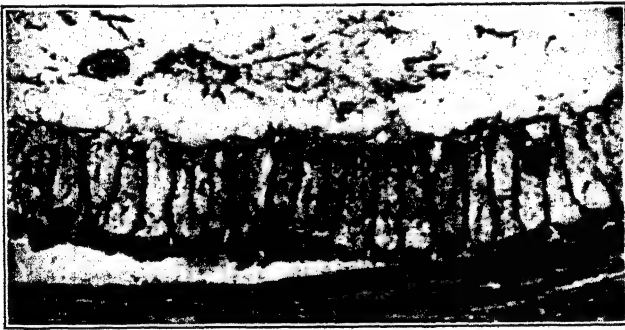


FIG. 378.—Pseudomucinous cystadenoma of the ovary. The palisade cells are filled with pseudomucin and the nuclei are displaced to the base.  $\times 500$ .

but these are seldom pronounced. In the exceptional cases where there is marked papillary formation there is danger of malignancy; such cases are often bilateral (Fig. 379).

There is a tendency to spontaneous perforation, but the pseudomucin seems to do little harm in the peritoneal cavity. In exceptional cases the tumor cells may become implanted on the peritoneum and produce large jelly-like masses, a condition known as *pseudomyxoma peritonei*. The prognosis is then bad, for the irritation of the new material sets up a chronic peritonitis, and repeated removal may fail to cure the patient.

**Serous Cystadenoma.**—This form, which constitutes about one-third of the cystic tumors of the ovary, may show different degrees of development. Thus there is the simple serous cyst which it may be difficult to distinguish from a large follicular cyst, the multiloculated serous cyst without papillary processes, and the multiloculated papillary serous cyst. The cystadenoma, which is frequently bilateral, resembles externally the pseudomucinous form, but it seldom has a well-developed pedicle. The *contents* of the cysts are clear and watery; they contain no pseudomucin, but are highly albuminous. *Microscopically* the cysts are lined by an epithelium which is low compared with that of the pseudomucinous variety, nor are the cells filled with pseudomucin. They are said usually to be ciliated.



FIG. 379.—Pseudomucinous cystadenoma with papillary formation.  $\times 60$ .

The most characteristic feature of these tumors is the presence of papillary processes, although these are not always present, so that the name papillary cystadenoma cannot be applied to the whole group. The presence of papillomata indicates a greater proliferative activity on the part of the epithelium, and the papillomata may appear on the outer as well as the inner surface, owing to invasion of the wall by the tumor cells (Fig. 380). This penetration does not prove that the condition has become malignant, but it is always suggestive. The papillary cystadenomas have a marked tendency toward malignant change, which is indicated by the soft character of the papillomata and the irregular arrangement of the epithelium. More or less of the original cyst structure may remain, with the malignant tissue represented by firm knobby areas, or the tumor, if highly cellular, may be soft and friable. In other cases the original cyst has been almost entirely

replaced by tumor, so that the mode of origin may be more than doubtful. The malignant change may only be recognized microscopically. The percentage of these tumors which become malignant varies in different statistics from 20 to 65. The mere fact that carcinoma is found in such a tumor does not mean that the prognosis is necessarily bad, for the malignancy is not high, the growth is often circumscribed, and removal may be followed by complete cure. Secondary papillomata may be scattered over the peritoneum producing an ascites which recurs repeatedly after tapping. The microscopic picture does not always correspond with the clinical course. There may be no microscopic evidence of malignancy, and yet the peritoneum may be covered with papillomata. On the other hand, cases of undoubted malignancy may run a very slow course and live as long as ten years. Calcification may sometimes occur; in one of my cases this involved a large area; it may even affect the glandular metastases.



FIG. 380.—Serous cystadenoma of the ovary. The contents appear unusually thick, the albumin having been coagulated by the fixative. Papillary processes are present on the inner and outer surfaces.

The *origin* of the serous cystadenoma is undoubtedly the germinal epithelium either on the surface or in the form of down-growths into the ovary. The ciliated nature of the epithelium shows its relation to the epithelium of the rest of the genital tract. The origin of the pseudomucinous form is not so obvious, for the type of epithelium of which it is composed does not occur in the normal ovary. Those who have studied the matter most closely believe that the lesion represents a one-sided development of a teratoma in which the tall, columnar, intestinal type of epithelium has replaced the other elements of the growth.

**Carcinoma.**—Carcinoma originating in the ovary is uncommon in comparison with metastatic carcinoma. The tumor is usually bilateral, one ovary being infected from the other. The tumor is of moderate size, and is usually soft and friable, though it may be firm if the stroma is abundant. The great majority of cancers of the ovary are malignant papillary cyst-

adenomas, although the papillæ may coalesce so as to give a solid appearance (Fig. 381). Thus a solid carcinoma may be a papillary cystadenoma which has become solid or it may be solid from the start. The latter may be of adenocarcinomatous or medullary type. The medullary form is usually composed of solid masses of carcinoma cells separated by a varying amount of stroma, but sometimes the cellular arrangement is diffuse and the structure highly anaplastic. Such tumors are easily mistaken for sarcoma, and their carcinomatous character is often not recognized.

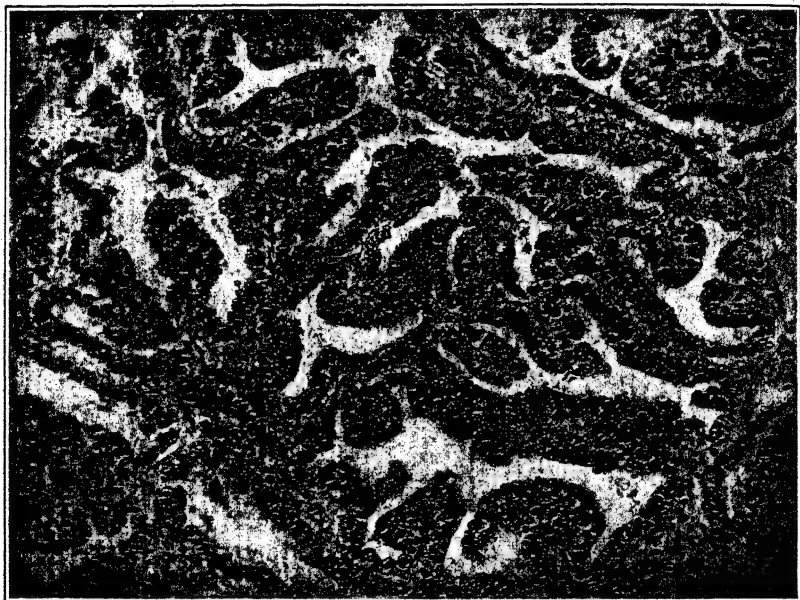


FIG. 381.—Papillary carcinoma of ovary.  $\times 100$ .

Metastases are scattered over the surface of the peritoneum, and are responsible for the hemorrhagic ascites which is characteristic of the condition, and in a woman should always suggest the possibility of cancer of the ovary. There may be metastases in the uterus owing to infection by way of the Fallopian tube. In such cases it may be difficult or impossible to be certain if the cancer started in the endometrium or the ovary, for both are derived from a common type of epithelium.

**SECONDARY CARCINOMA.**—These growths, which are nearly always bilateral, are of fairly frequent occurrence. The common primary sites are the stomach, large bowel, and uterus. The so-called *Krukenberg tumor* is characterized by large, round, vesicular cells with the nucleus pressed to one side by mucoid material so as to present a signet-ring appearance (Fig. 382), and separated by connective tissue showing mucoid degeneration. As a rule the primary tumor in the stomach or large bowel is a mucoid carcinoma, but this is not always the case. Apparently cancer cells growing in

the ovary may acquire an ability to produce mucin which they do not possess in the primary lesion. The route of infection probably varies. In some cases it is no doubt due to implantation of cancer cells on the surface of the ovary. On the other hand the tumors are usually in the interior rather than on the surface of the ovaries. Retrograde lymph spread to the lumbar nodes and thence to the ovaries is a reasonable explanation in most cases. Blood spread is an occasional possibility.

## SPECIAL OVARIAN TUMORS

Of recent years a group of solid ovarian tumors has been described, some uncommon, others very rare, but all characterized by a probable common origin from embryonic remnants (cell rests) and in some instances marked by sex hormone disturbances. Three of these (granulosa-cell tumor, arrhenoblastoma and dysgerminoma) have a common origin from the primitive mesenchyme of the ovary; the fourth (Brenner tumor) is unrelated.

In the developing ovary the granulosa layer of the follicles is formed by differentiation of the mesenchymal core of the gonad, not from the surface epithelium as used to be thought. The primitive granulosa cells are therefore connective tissue in type; only later do they develop an epithelial form. It follows that unripe tumors arising from these cells resemble connective tissue, whilst ripe tumors resemble epithelium; sometimes there may be a mixture of types.

The primitive gonad is neither ovary nor testicle, but may develop into either, the direction of development perhaps depending on the sex of the germ cells which invade the gonad from the primordial gut. Three errors of development are possible. (1) Embryonic rests of undifferentiated mesenchyme may remain and develop years later into a *granulosa-cell tumor*. Such a tumor will produce the female hormone with corresponding structural and functional disturbances. (2) In the primitive gonad male cells may be formed as a result of faulty development; these may remain as rests, and give rise in later life to an *arrhenoblastoma*, so-called because it produces a male hormone (*arrhen*, male) with corresponding functional disturbance. (3) Cells may be formed which do not develop along either a male or female line, and may be regarded as neuter. Years later these may give rise to tumors which naturally lack the power of producing hormones. In the ovary such a tumor is a *dysgerminoma*; in the testicle it is known as a seminoma. The *Brenner tumor* does not arise from the primitive mesenchyme of the ovary. Its origin is uncertain.

Much of the recent interest which has been aroused by these rare tumors is due to a series of papers by Robert Meyer. A summary of this work will be found in Novak's monograph.



FIG. 382.—Krukenberg tumor showing signet-ring cells.  $\times 275$ .



**GRANULOSA-CELL TUMOR.**—This tumor is also called granulosa-cell carcinoma, but in less than 30 per cent of cases has evidence of malignancy developed. The size varies greatly from 1 or 2 cm. in diameter to a mass the size of an infant's head. Usually unilateral, the outline is sharply defined, the outer surface smooth, and the cut surface has a characteristic yellow tinge but is sometimes gray. It may present cysts of varying size, although the smaller tumors as a rule are solid.

The *microscopic appearance* is confusingly varied, and as different parts of the tumor may differ in structure, it is important to cut a number of blocks. Three

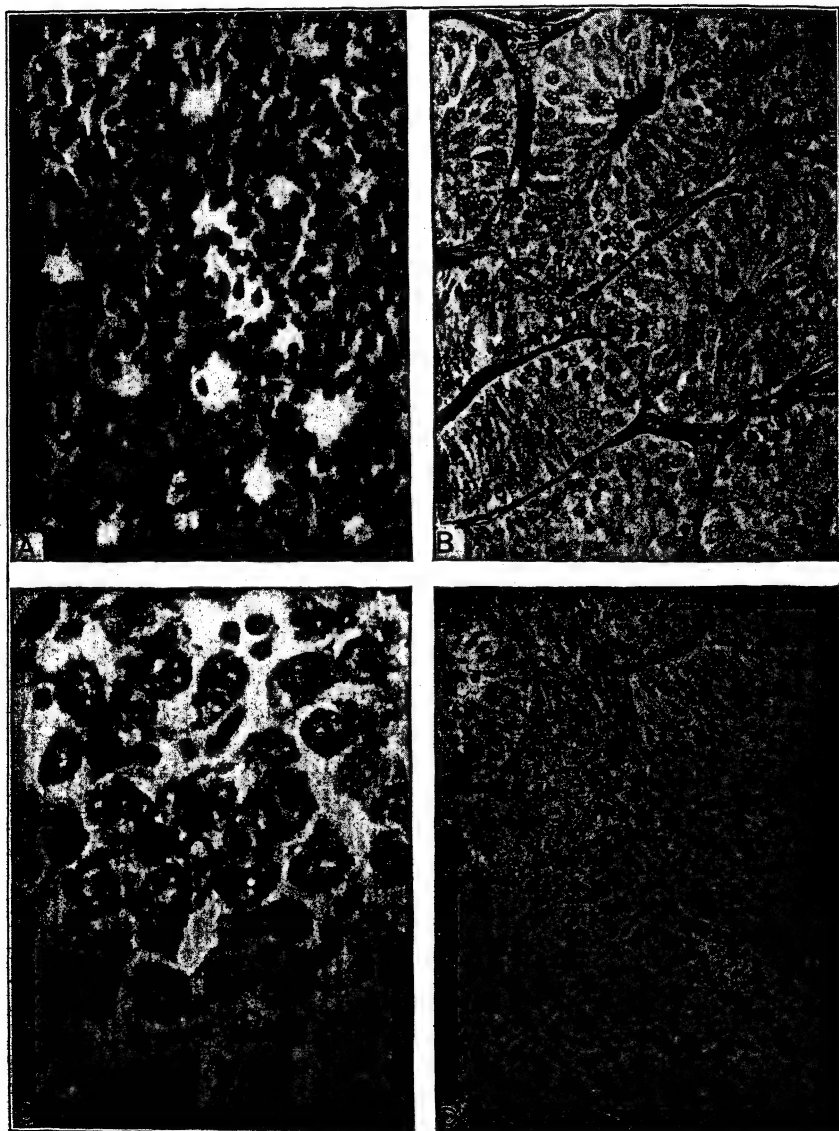


FIG. 383.—Special ovarian tumors: *A*, granulosa-cell tumor.  $\times 240$ ; *B*, arrhenoblastoma.  $\times 240$ ; *C*, dysgerminoma.  $\times 510$ ; *D*, Brenner tumor.  $\times 200$ .

main types may be distinguished: the follicular, diffuse, and cylindrical. In the *follicular type*, which is perhaps the most common, the granulosa cells are arranged in little clusters or rosettes around a central lumen (Fig. 383, A). To be distinguished from this lumen are the so-called Coll-Exner bodies, which are spaces in larger masses of granulosa cells produced by liquefaction. These spaces may contain bodies resembling and formerly mistaken for ova, but in reality they are secretion or degeneration products. In the *diffuse type* the granulosa cells are arranged diffusely rather than in rosettes. In the *cylindroid* or *cylindromatous* form masses of epithelial cells are separated by invasion and overgrowth of connective-tissue elements so that the appearance is one of anastomosing cylinders. Luteinization may occur, *i.e.*, an accumulation of lipid in the tumor cells. This is readily demonstrated by fat stains. The more marked is this process, the more striking is the yellow color of the tumor. When the process is widespread the tumor is spoken of as a luteoma.

The *malignancy* is variable. Most cases pursue a benign course, the tumor often being found incidentally. In other cases there may be peritoneal recurrence a few months after removal of the tumor. The microscopic picture is of no value in determining the degree of malignancy.

Occasional tumors of this series present a connective-tissue appearance and are known as *theca-cell tumors*. The tumor, which is hard and fibrous, consists of interlacing bands of spindle cells rich in doubly refractive lipid and therefore giving the tumor a yellow color.

The *genesis* of these tumors is usually considered to be granulosa-cell rests which have not been used in the process of follicle formation. When one considers the intimate relationship which exists between the granulosa-cell and theca-cell tumors, it seems more probable that their origin may be traced to primitive mesenchyme which antedates the differentiation of granulosa and theca cells.

The *clinical effects* of what has been called the feminizing tumor depend on the period of life at which the tumor develops. The granulosa cells produce estrogenic hormone, so that there will be abnormal menstrual bleeding before puberty or after the menopause, but during the reproductive years the only effect is likely to be increase in the flow. In the child there will be precocious puberty, *i.e.*, early menstruation, development of the breasts and external genitalia, and hypertrophy of the uterus. In the adult endometrial hyperplasia may be a marked feature. Carcinoma of the endometrium has developed in a number of cases, a point of interest in connection with the relation of sex hormones to carcinogenesis. Removal of the tumor in the prepuberty and postmenopausal cases is followed by disappearance of the abnormal clinical features.

**ARRHENOBLASTOMA.**—This masculinizing tumor is the rarest member of the special ovarian tumors. It arises from the cells of the primitive ovarian mesenchyme which have a male tendency, and it is often found in the region of the rete

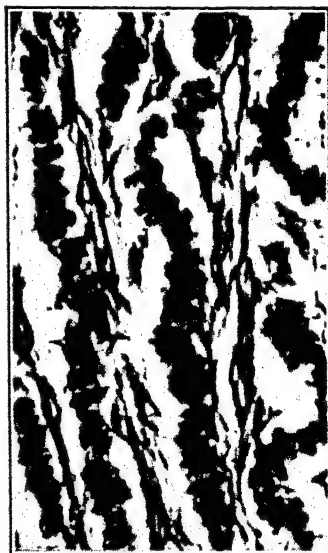


FIG. 384.—Arrhenoblastoma showing step-ladder arrangement of cells.  $\times 220$ .

ovarii, which is the homologue of the male testis. The gross appearance is similar to that of the granulosa-cell tumor. The *microscopic* picture varies even more widely than that of the latter tumor. In some cases, but these are the exception, there is perfect reproduction of the seminiferous tubules of the testis, a condition described long ago by Ludwig Pick as testicular adenoma of the ovary (Fig. 383, B). More usual is a very imperfect attempt at tubule formation, the cells being arranged for the most part in irregular columns. The nuclei often show a step-ladder arrangement which may suggest to the observer the true nature of the tumor (Fig. 384). At the far end of the scale the cells are completely undifferentiated, giving a picture of sarcoma. In such cases the pathologist is dependent on the characteristic clinical history. In spite of the sarcomatous appearance the tumor is either benign or of low malignancy.

The *clinical effects* are at first defeminizing, later masculinizing. Amenorrhea and extreme atrophy of the breasts are the early signs. These are followed later by hirsutism with masculine distribution of hair, roughening and deepening of the voice, and hypertrophy of the clitoris. The picture is similar to that of tumor of the adrenal cortex, a structure with which the ovary is closely related developmentally.

**DYSGERMINOMA.**—This tumor, the name of which is also spelt disgerminoma, arises from indifferent cells of the mesenchyme in the gonad which fail to develop in either a male or female direction. It may occur in the ovary or testis. In the ovary it is often bilateral, may grow to a considerable size, and shows a characteristic yellow staining of the cut surface due to lipoid degeneration.

*Microscopically* the tumor is simple in structure, and does not show the marked variation characteristic of the granulosa-cell tumor and arrhenoblastoma. The cells are large and round with vesicular nuclei (Fig. 383, C), but they shrink to a marked degree when embedded in paraffin, and are best seen in frozen or celloidin sections. They are grouped in solid alveoli or in columns, separated by septa of fibrous tissue in which there may be large numbers of lymphocytes.

These tumors vary greatly in malignancy, nor does the microscopic picture help much in the prognosis, although the presence of numerous mitoses is of course a bad sign. The tumor is less malignant than the granulosa-cell tumor but more malignant than the arrhenoblastoma. In about 25 per cent of cases there are extrapelvic metastases.

The *clinical effects* are in striking contrast to those of granulosa-cell tumors and arrhenoblastoma, as might be expected from the fact that the tumor originates from indifferent sex cells. It usually arises in children and adolescents, but may occur in adults. As a rule the patient is normal sexually, but in a number of cases there has been pseudohermaphroditism, sexual hypoplasia or infantilism. This disturbance of development does not appear to be dependent on the presence of the tumor, because after surgical removal there has been no change in the clinical condition.

**BRENNER TUMOR.**—The lesion, described by Brenner in 1907, but clarified by Robert Meyer in 1932, differs sharply from the group of three "special" ovarian tumors already discussed. In the gross the tumor may take two forms, solid or cystic. The solid form, which is the usual type, tends to be small and resembles a fibroma, for which it is readily mistaken. When large, for reasons which soon will be apparent, it may take the form of pseudomucinous cystadenoma with nodular masses of tumor persisting in the wall. There are wide variations in size; it may be minute or it may be enormous.

The *microscopic picture* has none of the extreme variability so characteristic of granulosa-cell tumor and arrhenoblastoma. There are two essential elements: (1) nests of epithelial cells, and (2) fibromatous connective tissue separating these

nests (Fig. 383, D). The epithelial cells are for the most part strikingly uniform in type, and recall the appearance of a carcinoid tumor of the appendix or bowel. There are no mitoses, nor any suggestion of malignancy. Cystic degeneration in the center of the nests is common, giving rise to an appearance which may be mistaken for follicles. One striking variation from the usual picture may occur, the cells becoming columnar and clear, secreting mucus, and lining spaces, a picture similar to that of a pseudomucinous cystadenoma. When this condition is widespread, the gross appearance may be identical with the ordinary cystadenoma, and the essential character of the original tumor may be overlooked. The connective-tissue elements vary, but may be so abundant that the lesion is mistaken for a fibroma.

The *origin* of the tumor is still a matter of dispute. The commonly accepted view is that of Meyer, who believes that the starting point is the so-called Walthard inclusions. These are minute circumscribed nests of cells which are found in the new-born and young child. Occasionally these take the form of gland-like spaces lined by columnar epithelium which may secrete mucus. Other suggestions are a dislocation of cells from the primitive urogenital tract, and one-sided development of a teratoma, the latter based on the frequent association with pseudomucinous cystadenoma.

The tumor is rare, but many cases must be overlooked. It is benign, of slow growth, and the majority are detected over the age of fifty. There is no endocrine disturbance.

**BERGER TUMOR.**—This tumor arises from cells at the ovarian hilus which are androgenic in function and are analogous to the Leydig cells of the testis. Both sets of cells contain lipids, lipochrome pigment, and the peculiar and characteristic rod-like structures known as the crystalloids of Reinke. It was Berger who in 1922 first recognized the significance of these hilar cells and their identity with the similar cells of the testis. He named them sympathiotropic cells because of their constant relationship to the nonmyelinated nerves of the hilus, the cells ensheathing the nerve fibers, and sometimes lying within a nerve trunk. Berger was also the first in 1942 to report a case of masculinization associated with a small tumor of ovarian hilus cells. In view of the fundamental contributions which Berger made to the subject over a period of twenty years it seems fitting and proper to attach his name to the tumor. An alternative name is tumor of the sympathiotropic cells of the ovarian hilus. The pathognomonic feature is the presence of intracellular Reinke crystalloids (Fig. 385). These tumors in the past have been mistaken for other masculinizing tumors of the ovary such as arrhenoblastoma and adrenal rest tumors.

**Dermoid Cyst.**—This is a teratoma, and is one of the common tumors of the ovary. In about 10 per cent of cases it is bilateral. It is of slow growth, and is almost invariably innocent, but in rare cases one of the elements of which it is composed may undergo malignant change. Its appearance is very characteristic, for it is of a yellow color and of a doughy consistence when removed from the body, although at body temperature the contents are fluid. The *contents* consist of a yellow, greasy, buttery material containing a considerable amount of hair. The wall, which is lined by cubical epithelium, gives rise at one place to a nipple-shaped process covered by stratified epithelium and known as the *dermoid process*. This is the real tumor, for the other solid elements are derived from it. The commonest of these are skin and hair (hence the name dermoid), but bone, teeth, cartilage, brain, intestine, striated muscle, thyroid, adrenal, etc., may occur. In exceptional cases the thyroid tissue may proliferate to such a degree that the tumor consists almost entirely of this tissue. Such

a condition is known as *struma ovarii*. It will be seen that the tumor contains constituents derived from all three germinal layers, and is therefore a true teratoma. The oily material which distends the cyst is produced by the numerous sebaceous glands with which the skin of the dermoid process is studded (Fig. 386). A dermoid begins as a solid tumor, and the cyst formation is secondary.

The dermoid cyst and the solid ovarian teratoma are commonly supposed to arise from one of the original blastomeres formed by the primary segmentation of the ovum, which has become separated and included in the ovary. It appears equally or even more probable that the tumor arises from one of the sex cells (ova) of the ovary.

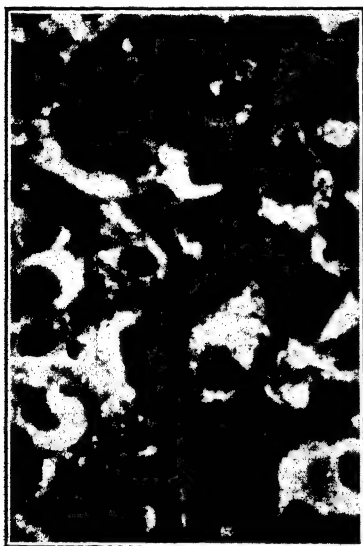


FIG. 385.—Reinke crystalloid in Berger tumor.  $\times 670$ .



FIG. 386.—Dermatoid cyst showing stratified epithelium and sebaceous glands.  $\times 60$ .

**SOLID OVARIAN TERATOMAS.**—Solid ovarian teratomas are very rare tumors. They contain no fully formed structures such as skin and bone, but a variety of tissues usually in a rudimentary state, although well formed thyroid and other structures are sometimes present. They form soft solid masses which are highly malignant.

**FIBROMA.**—Fibroma of the ovary is rare. Many of the lesions which used to be regarded as fibroma are now known to be examples of Brenner's tumor. It is a small, hard, white circumscribed tumor, and may arise in some cases from a corpus albicans.

**SARCOMA.**—Sarcoma is very rare. Most of the tumors taken for sarcoma are probably anaplastic carcinomas. True sarcomas may occur as bilateral tumors in children, and present the usual soft homogeneous appearance of a sarcoma. They are composed of round undifferentiated cells.

**MEIGS' SYNDROME.**—This term denotes a strange association of ascites, hydrothorax (usually right-sided), and a tumor of the ovary, usually but by no means invariably fibroma. Ascites is said to develop in association with 40 to 70 per cent of ovarian fibromas. Many theories have been suggested to explain the ascites and the less common hydrothorax. Rubin and his associates, recalling an old observation of Geibel's that an ovarian fibroma weighing 3200 grams lost 1150 grams of water in twenty-four hours, adduce evidence in support of the view that the fluid comes from the numerous and large lymphatics at the hilum of the ovary. As ovarian tumors are covered by a single layer of low highly permeable epithelium, the fluid may readily escape. Transfer from the abdominal to the pleural cavity may be through the channels which connect the lymphatic networks on both sides of the diaphragm.

**HYPERNEPHROID TUMORS.**—One of the rarest of ovarian tumors is yellow in color and presents a picture of carcinoma composed of clear cells like those of hypernephroma. They are therefore called hypernephroid tumors, and are supposed to arise from mesonephric structures within the ovary (Saphir and Lackner).

### PAROVARIAN CYSTS

The parovarium, which represents a remnant of the sexual part of the Wolffian body, is situated in the mesosalpinx between the ovary and the Fallopian tube. It consists of a horizontal tube, the duct of Gartner, homologous with the vas deferens, and a series of vertical tubes homologous to the vasa efferentia and epididymis. A parovarian cyst is situated between the layers of the broad ligament and may attain a great size. The wall is thick and lined by low, columnar, ciliated epithelium. Sometimes it shows warty papillary processes, but usually it is quite smooth. As the cyst occupies the broad ligament it may be mistaken for a serous cyst-adenoma of the ovary growing in that position. The intact ovary is attached to the side of the cyst, and the tube is stretched over the cyst and is greatly elongated. The condition is always innocent.

The so-called hydatid of Morgagni is a minute pedunculated cyst attached to the fimbriated end of the Fallopian tube. It is present in some 8 per cent of adults and is of no clinical importance. It appears to arise from the outer part of the epoöphoron (parovarium).

### THE VAGINA AND VULVA

**SOFT CHANCRE.**—Soft sore is an acute inflammatory venereal lesion which takes the form of multiple small ulcers over the external genitalia. They are shallow and have none of the induration so characteristic of syphilitic lesions. There is a marked tendency to the formation of suppurating buboes in the groin.

**SYPHILIS.**—A syphilitic lesion of the vulva may be primary or secondary. The primary lesion presents the usual appearance of a hard chancre, except that not infrequently there are lesions on both labia minora due to contact infection. The secondary lesions are mucous patches and condylomata.

**CONDYLOMA ACUMINATUM.**—This is a warty or papillary lesion, called "acuminatum" because of its pointed form compared with the broad condylomata of syphilis. These warts, which cover the labia, are venereal in origin, being almost always due to gonorrhea. Microscopically there is hypertrophy of the connective-tissue papillæ of the skin, which grows outward, producing a warty appearance. The epithelium covering these processes is also thickened.

**TRICHOMONAS VAGINALIS INFECTION.**—Vaginal infection with *Trichomonas vaginalis* is being reported with increasing frequency. It is especially common in pregnant women, but is not confined to that state. The parasite is a pear-shaped flagellate measuring 7 to 30 microns in length, seen with great ease and vividness in the dark field. For this purpose the discharge is collected in a capillary pipette, which is placed in a test tube and sent at once to the laboratory. The patient may have an acute inflammation of the vagina, with a profuse seropurulent discharge which is often foamy or bubbling, and contains large numbers of bacteria and flagellates. There is still difference of opinion regarding the pathogenicity of the parasite.

**LEUKOPLAKIA AND KRAUROSIS.**—*Leukoplakia* of the vulva may occur in the later years of life and is usually associated with intense pruritus. There is marked thickening of the epidermis, this thickening including both the stratum corneum and stratum Malpighi. The great clinical importance of the condition is that it is often precancerous, and may develop into epidermoid carcinoma. *Kraurosis vulvæ* (*krauros*, dry) is a closely related condition characterized by marked shrinkage of the external genitalia which become dead white and wrinkled like parchment. The stratum corneum is thick, but the stratum Malpighi is very thin and atrophic, the papillæ disappear, and the epidermis takes the form of a narrow straight band. Chronic inflammatory cells are present in the underlying tissue. The lesion is often associated with leukoplakia, and may be regarded as a variety of that condition. Occasionally it is precancerous.

**TUMORS.**—*Carcinoma of the vulva* is not uncommon. It is nearly always preceded by some precancerous condition such as leukoplakia, kraurosis, gonorrheal warts, or other evidence of chronic inflammation. It is epidermoid in type, and early metastases occur in the inguinal lymph nodes. *Carcinoma of the vagina* is less common; it presents the same characteristics. *Mixed tumor of the vagina*, so-called sarcoma of the vagina, is the same tumor as the "grape-like sarcoma" of the cervix. It is a malignant tumor of children, and is composed of mucoid tissue, plain and striated muscle, etc. Owing to mucoid degeneration many cyst-like structures may be formed.

**URETHRAL CARUNCLE.**—This not uncommon condition takes the form of a small, bright red, exquisitely tender, polypoidal mass which arises from the opening of the urethra and projects into the vestibule. Its structure varies, but it may be regarded as a capillary angioma, consisting of telangiectatic or highly vascular connective tissue infiltrated with round cells and covered by squamous epithelium.

## CONGENITAL ANOMALIES OF FEMALE GENITAL TRACT

A great variety of defects may occur in the course of the development of the female genital tract. Only the more common ones can be referred to here. For further details works on gynecology must be consulted.

**UTERUS.**—The uterus and vagina are formed by fusion of the lower part of the Müllerian ducts, the upper parts remaining separate to become Fallopian tubes. This fusion may be incomplete, so that there may be a double uterus and vagina, a single vagina and double uterus, or the uterus may only be divided in its upper part so that it seems to have two horns (*uterus bicornis*). Splitting of the upper part of the Müllerian ducts gives rise to two Fallopian tubes on each side. *Hypoplasia* (persistence after birth of the infantile type of uterus) is part of a general infantilism, such as occurs from thyroid or pituitary deficiency. *Absence of the uterus* is very rare. *Atresia* or closure of the os leads to an accumulation of menstrual blood in the uterus. If one of the Müllerian ducts does not develop, there will be absence

of one of the tubes and the uterus is asymmetrical. Persistence of portions of the Wolffian ducts in the wall of the vagina may lead to the formation of cysts and tumors.

**OVARIES.**—Hypoplasia of the ovaries is associated with general hypoplasia of the genital system. The ovary may be displaced, *e.g.*, in a patent canal of Nuck. Displacement of the germinal epithelium may occur, and it is possible that the common cystadenomas of the ovary may arise from such displaced portions.

## ADDITIONAL READING

- Adenomyoma.** CULLEN: *Adenomyoma of the Uterus*, Philadelphia, 1908.
- Berger Tumor.** BERGER: *Compt. rend. Acad. d. sc.*, 1922, 175, 907; *Rev. Can. de Biol.*, 1942, 1, 539. STERNBERG: *Am. J. Path.*, 1949, 25, 493. WAUGH, *et al.*: *J. Clin. Endocrinol.*, 1949, 9, 486.
- Brenner Tumor.** GAINES: *Am. J. Obst. and Gynec.*, 1936, 32, 457. NEIMAN: *Arch. Path.*, 1936, 21, 55. NOVAK AND JONES: *Am. J. Obst. and Gynec.*, 1939, 38, 872. PLAUT: *Arch. f. Gynäk.*, 1932, 148, 541.
- Carcinoma of Cervix.** GARDNER, *et al.*: *J. A. M. A.*, 1938, 110, 1182. HEALY AND CUTLER: *Am. J. Obst. and Gynec.*, 1928, 16, 15. HOFBAUER: *Am. J. Obst. and Gynec.*, 1933, 25, 779; 1934, 27, 633. MARTZLOFF: *Bull. Johns Hopkins Hosp.*, 1927, 40, 160. PAPANICOLAOU: *J. A. M. A.*, 1946, 131, 372.
- Chorionepithelioma.** SIMARD: *Am. J. Cancer*, 1937, 30, 298.
- Dysgerminoma.** SAILER: *Am. J. Cancer*, 1940, 38, 473.
- Endometrial Histology.** CAMPBELL, *et al.*: *Surg., Gynec. and Obst.*, 1936, 63, 724.
- Endometrial Hyperplasia.** BURCH, *et al.*: *Surg., Gynec. and Obst.*, 1931, 53, 338. FLUH-MANN: *Surg., Gynec. and Obst.*, 1931, 52, 1051.
- Endometrial Stromatosis.** HENDERSON: *Am. J. Obst. and Gynec.*, 1946, 52, 1000.
- Endometriosis.** BLOCK: *Am. J. Med. Sci.*, 1940, 199, 579. GOODALL: *A Study of Endometriosis, Endosalpingiosis, Endocervicosis, and Peritoneo-ovarian Sclerosis*, Philadelphia, 1942. JACOBSEN: *Arch. Path.*, 1928, 5, 1054. KING: *Surg., Gynec. and Obst.*, 1931, 53, 22. MACLEOD: *Brit. J. Surg.*, 1946, 34, 109. SAMPSON: *Arch. Surg.*, 1921, 3, 245. WELLER: *Am. J. Path.*, 1935, 11, 287. WITHERSPOON: *Arch. Path.*, 1935, 20, 22.
- Fibrosis Uteri.** BAKER: *Am. J. Path.*, 1933, 9, 369.
- General References.** FRANK: *Gynecological and Obstetrical Pathology*, 2nd ed., New York, 1931. LYNCH AND MAXWELL: *Pelvic Neoplasms*, 2nd ed., New York, 1931. NOVAK: *Gynecological and Obstetrical Pathology*, 3rd ed., Philadelphia, 1952.
- Granulosa-cell Tumor.** NOVAK: *Am. J. Obst. and Gynec.*, 1933, 26, 505. NOVAK AND LONG: *J. A. M. A.*, 1933, 101, 1057.
- Hypernephroid Tumors of Ovary.** SAPHIR AND LACKNER: *Surg., Gynec. and Obst.*, 1944, 79, 539.
- Intraepithelial Carcinoma of Cervix.** HOWARD, *et al.*: *Am. J. Path.*, 1949, 25, 794.
- Meigs' Syndrome.** GARDINER AND HAERT: *Lancet*, 1944, 2, 500. MEIGS, *et al.*: *Am. J. Obst. and Gynec.*, 1943, 46, 19.
- Menstruation.** CORNER: *Medicine*, 1933, 12, 61. NOVAK: *Menstruation and Its Disorders*, 2nd ed., New York, 1931.
- Ovarian Cysts of Infants.** SPIVACK: *Am. J. Obst. and Gynec.*, 1934, 27, 157.
- Special Ovarian Tumors.** KARSNER: *Tr. and Stud. Coll. Physicians, Philadelphia*, 1940, 7, 301. MEYER: *Am. J. Obst. and Gynec.*, 1931, 22, 697. SCHILLER: *J. Obst. and Gynec.*, *British Emp.*, 1936, 43, 1135.
- Toxemia of Pregnancy.** BAIRD AND DUNN: *J. Path. and Bact.*, 1933, 37, 291. BELL: *Am. J. Path.*, 1932, 8, 1. DEXTER, WEISS AND OTHERS: *Preëclampsic and Eclampsic Toxemia of Pregnancy*, Boston, 1941.
- Tubal Changes of Menstrual Cycle.** NOVAK AND EVERETT: *Am. J. Obst. and Gynec.*, 1928, 16, 499.
- Utero-placental Apoplexy.** STANDER: *Williams Obstetrics*, 8th ed., New York, 1941. WILLIAMS: *Surg., Gynec. and Obst.*, 1915, 21, 541.
- Vaginal Smear in Uterine Cancer.** MEIGS, *et al.*: *Surg., Gynec. and Obst.*, 1943, 77, 449. PAPANICOLAOU AND TRAUT: *Diagnosis of Uterine Cancer by the Vaginal Smear*, New York, 1943.



## THE BREAST

**PATHOLOGICAL PHYSIOLOGY.**—Just as the endometrium is not a static structure but shows cyclic changes due to ovarian stimulation, so also does the breast. Indeed there is no organ which shows a wider range of structural variation in health. Up to the time of puberty the parenchyma consists only of ducts. At puberty under the influence of estrin active budding of the ducts occurs, and from these buds the acini are formed. It is during pregnancy and lactation that the changes are most marked. The breast in pregnancy consists of a mass of glandular tissue which entirely replaces the fat. When the placental stimulus is withdrawn lactation (secretion) begins, and this is accompanied by a marked invasion of lymphocytes. After lactation comes involution, but this is never complete and the glandular overgrowth does not entirely disappear. At the menopause the glandular tissue is replaced by connective tissue.



FIG. 387.—Gland fields of the breast. Six units are shown, each consisting of a group of ducts surrounded by specialized pale connective tissue. Changes in these units are the basis of cystic hyperplasia and fibroadenoma.  $\times 75$ .

During each menstrual cycle these structural changes are reproduced in miniature. The normal virgin breast in the intermenstrual period consists of a small number of ducts with rudimentary acini. These are surrounded by a specialized loose connective tissue, the periductal tissue, which is under hormonal influence and is quite distinct from the general stroma of the breast. The combined glandular and specialized connective tissue form a series of islands known as lobules or gland fields (Fig. 387). Only a certain proportion of the gland fields undergo cyclic men-

strual changes. At the menses some of the epithelial cells are desquamated, the remainder atrophy and there is shrinkage of the ducts. A few days after the period the duct system begins to proliferate, the epithelial cells increase in size and number, and there is development of soft, pale, periductal connective tissue, mucoid in character and infiltrated with lymphocytes. Wide morphological variations may occur, which are beautifully illustrated in Helen Ingleby's paper.

The infinitely delicate balance between the ovarian hormonal stimuli is easily upset, and this upset is reflected in the mirror of the breast. The ducts become hypertrophied and dilated and the connective tissue is increased. These changes may be within physiological limits, when the condition is known as *mazoplasia*, or they may form the basis of such pathological lesions as cystic disease of the breast, fibroadenoma and duct papilloma (Fig. 388).



FIG. 388.—Section of breast showing a combination of cystic hyperplasia and fibroadenoma.  $\times 40$ .

**CYSTIC HYPERPLASIA OF THE BREAST.**—This, the commonest structural lesion of the breast, is an exaggeration of the physiological changes outlined above. Countless names have been attached to the condition over the years. The surgeon sticks to the old name, chronic mastitis, although this is in no sense an inflammation of the breast. One of the best terms is lobular hyperplasia with or without cyst formation (Smith). This was used in previous editions of this book, but it has never been generally accepted. Cystic hyperplasia is admittedly inadequate, as there may be no gross cysts but merely dilation of the ducts. It is, however, a convenient makeshift. The basis of the condition is hormonal imbalance, probably corpus luteum deficiency combined with hyperestrinism. It is,

therefore, chiefly seen in the last decade of reproductive life, but the main symptoms may not appear till after the menopause.

**CLINICAL FEATURES.**—The patient is usually in the involutionary period of life, at a time when the ovarian function is irregular and declining. Another group is seen in young unmarried women who often present evidence of disturbance of ovarian function. They really suffer from hypoactivity of the ovaries (short and scanty menstruation) with overactive or persistent corpora lutea. The condition is commoner in multiparæ, whose breasts have repeatedly passed through the periodic hyperplasia and involution of pregnancy and lactation. The woman complains either of pain or a lump in the breast; the pain is usually worse at the menstrual period. There is tenderness as well as pain. Both breasts are often involved, and there may be several lumps in each breast, which always suggests an innocent condition. The breast may feel coarsely granular owing to the presence of small cysts; such cysts always feel as hard as a tumor, never soft and fluctuating. The axillary lymph nodes may be enlarged and tender for a reason which is not obvious.

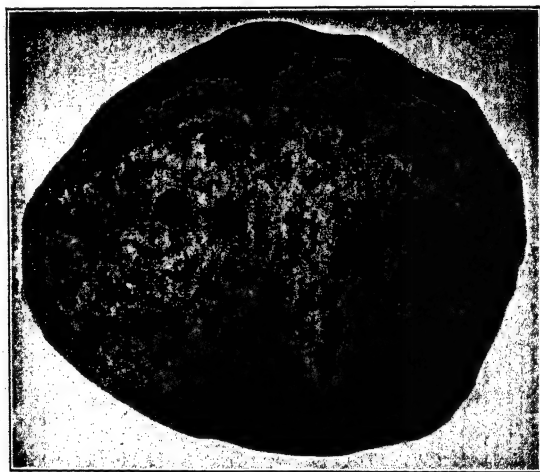


FIG. 389.—Cystic hyperplasia. All of the tissue shown is the seat of a diffuse induration. There are several cysts of varying size and many very minute cysts.

The *gross appearance* is characteristic, and it is usually easy to make a naked-eye diagnosis when the specimen is removed in the operating room. As the involvement of the lobules is so variable the condition may be general or local, and each of these may be cystic or non-cystic, at least to the naked eye. The generalized cystic form is known as Schimmelbusch's disease, in which the breast may be riddled with large smooth-wall cysts. Sometimes there is a single large cyst tensely filled with fluid and known as the blue-domed cyst (Bloodgood). Cysts of varying size and number are usually present (Fig. 389), but usually they are small. The cause of the cyst formation is obscure. The dilated ducts may be filled with putty-like material which can be squeezed out like worm casts. The lesion is characteristically tough and india-rubbery in consistence, but without the hardness of carcinoma, nor has it the circumscribed character of a malignant mass, shading off into the surrounding tissue. The color is gray.

The varied *microscopic picture* presents one or more of the following features: (1) *Glandular hyperplasia* is usually marked as evidenced by the number and prominence of the gland fields. The acini are represented by solid buds of cells which stain darkly. This appearance is likely to be found in younger women. (2) *Cyst formation* is so common that it has been incorporated in such names as cystic mastitis (Fig. 390). The cysts are usually small, they may be microscopic in size, or they may be as large as a cherry. The cysts are formed from the ducts, not as the result of obstruction by fibrous tissue nor distention by secretion, but because the hyperplastic duct has not undergone complete involution to the normal size. When a cyst is once formed, secretion may add to its size. (3) *Papillary formation* may be very striking owing to the epithelial cells growing in bud-like formation into the cyst spaces. This intraductal epithelial proliferation may progress to such a degree that the entire lumen



Fig. 390.—Cystic hyperplasia. Both epithelial proliferation and cyst formation are present. There is commencing papillary formation in the large cyst.

becomes packed with cells. It may be very difficult to distinguish this condition from carcinoma, and in some cases actual invasion of the surrounding tissue may occur. (4) *Acidophilic epithelial cells* may line the cyst or form the papillary processes (Fig. 391). Part of a cyst may be lined by normal cells, and part by these large cells, the cytoplasm of which stains pink with eosin. The change appears to be due to hyalinization of the epithelium. The cytoplasm of these cells when suitably stained is found to be filled with granules, and the appearance of the cells is identical with that of the cells of the specialized apocrine sweat glands in the axilla and elsewhere (Lendrum). Both mammary epithelium and the epithelium of apocrine glands arise from primitive sweat gland epithelium, and the mammary epithelium may become dedifferentiated to the primitive sweat gland type, and in the subsequent regeneration acquire the characteristics of apocrine sweat gland epithelium. Bunting, on the other hand, has shown that true apocrine sweat glands with eosinophilic epithelium are normal constituents of the breast, presenting the same patterns of lipid and iron

which are characteristic of the apocrine glands in the axilla and elsewhere. (5) *Connective-tissue hyperplasia* is an integral part of the process, but varies greatly in amount. It is the specialized connective tissue of the gland fields which is involved, not the stroma of the breast. The overgrowth may



FIG. 391.—Cystic hyperplasia with papillary formation. The papillary epithelium stained pink with eosin.  $\times 90$ .

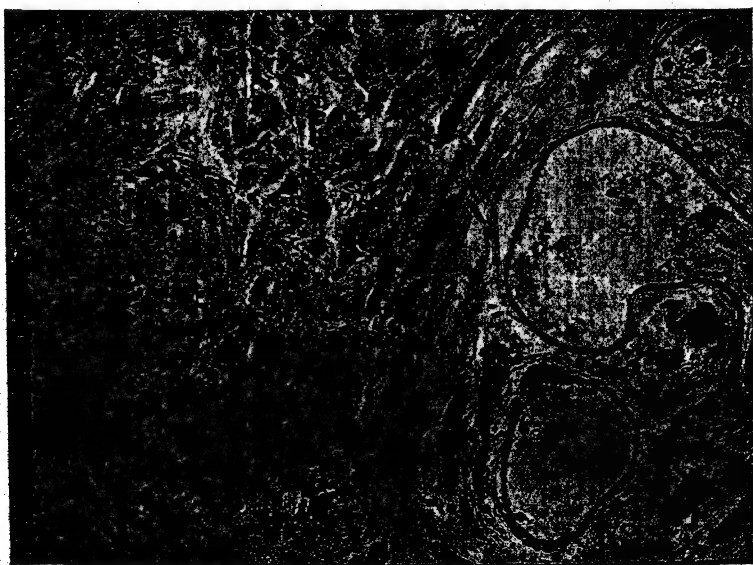


FIG. 392.—Carcinoma of the breast associated with cystic hyperplasia. (From Boyd's Surgical Pathology.)

be so great that the condition is practically one of pericanalicular fibroma. (6) *Lymphocytic infiltration* is a very common feature, and is responsible for the misconception that the condition is a mastitis.

**RELATION TO CARCINOMA.**—The question of the relation of cystic hyperplasia to carcinoma is a very difficult one, regarding which there are great differences of opinion. The condition is commonly regarded as precancerous and a radical operation is often done lest a worse thing should befall the patient. This may be advisable in an elderly patient, but is certainly unjustifiable in a young woman. The writer feels that from the pathological point of view it is possible to trace a long series of progressive changes in the duct epithelium, until the ducts are filled with masses of cells which are indistinguishable histologically from cancer cells and which may finally break through the wall and invade the surrounding tissues (Fig. 392). Actively proliferating lesions such as intraduct papilloma and cysts with papillary epithelium are of graver import than large cysts with atrophic epithelium. Greene has observed a strain of rabbits many of whom developed cystic disease of the breast followed by carcinoma. The cystic disease phase was identical with Schimmelbusch's disease in women. Within the cysts there occurred first epithelial hyperplasia, then neoplasia, and finally invasion. These changes were watched by means of repeated biopsies. From the pathological standpoint, therefore, the condition must be regarded as precancerous. The final court of appeal should be follow-up studies on women who have had complete (but not radical) removal of the gross lesion. Unfortunately there is no unanimity on this point in the published reports. Bloodgood, and more recently Campbell, conclude from such studies that there is no causal relationship between the two conditions, although both are common lesions of the breast occurring mostly at the same age period. Shields Warren, on the other hand, as the result of similar studies, believes that a woman who has had chronic mastitis is in far greater danger of developing cancer, even though all the apparently abnormal tissue has been removed, but once she has passed the menopause there is no greater danger than in any control group. If a malignant change does occur it is apparently of a limited character, which differs markedly from the invasive character of an ordinary primary carcinoma in which early removal is often of no avail.

**FIBROSING ADENOMATOSIS.**—Ewing has drawn attention to this condition which he says gives rise, probably more frequently than any other lesion of the breast, to a mistaken diagnosis of cancer. It is commoner in young women. The breast contains a number of hard discrete nodules, the cut surface of which is uniform in contrast with that of carcinoma. The microscopic appearance is described by the name, for there is multiplication of the acinar cells combined with fibrosis, the latter dominating the picture and finally leading to atrophy. There is a tendency for the acini to break up into small groups and clumps of cells. The picture is a characteristic one. The condition bears no relation to malignancy.

### FIBROEPITHELIAL TUMORS

When the hyperplasia which is characteristic of aberrant breast physiology is localized, a nodular condition is produced which is commonly

regarded as a tumor. The hyperplastic area may be semi-encapsulated, being sharply demarcated on one side but continuous with the breast tissue on the other. The hypertrophy may be great enough to push the fibrous tissue aside so that a complete capsule is formed. If the overgrowth chiefly affects the connective tissue we speak of a *fibroma*. As a rule both epithelial and fibrous tissues share in the overgrowth, giving a *fibroadenoma*. Localized epithelial overgrowth into a dilated duct forms a *duct papilloma*.

**Fibroadenoma.**—A fibroadenoma occurs chiefly in young women, originating perhaps at puberty and growing during the years of developing sexual activity. It is commoner in nulliparæ than in those who have borne children, differing in this respect from cystic hyperplasia.



FIG. 393.

FIG. 393.—Intracanalicular fibroadenoma. The process of formation is shown here, but usually no connection can be seen between the mass within the duct and the surrounding wall.  $\times 175$ .



FIG. 394.

FIG. 394.—Intracanalicular fibroadenoma of the breast. The ducts are elongated and distorted by the new fibrous tissue.  $\times 75$ .

It is customary to recognize two forms of tumor, the intracanalicular and the pericanalicular. The *intracanalicular fibroadenoma* is the common variety (Fig. 393). As the hyperplasia involves particularly the specialized connective tissue of the lobules, the tumor is more a fibroma than an adenoma. It is usually well encapsulated, has a soft consistency and a rather moist appearance, and the cut surface may show many narrow slits or splits (the ducts), so that the appearance may resemble the leaves of a book; sometimes little masses can be distinguished enclosed within small

spaces. The encapsulation may be only partial, the tumor blending on one side with the surrounding breast tissue. *Microscopically* there is a great proliferation of loose connective tissue of open structure which invaginates the wall of the ducts, projecting into the lumen to form polypoid masses, and producing great dilatation, elongation, and distortion of the ducts (Fig. 394). The connection of these polypoid growths with the wall of the duct is often not seen in the section, so that fibrous masses covered by a layer of epithelium appear to be lying free in the lumen. The ordinary connective stroma of the breast takes no part in the overgrowth. The lobules of the surrounding tissue often show hyperplasia, and in those cases where the encapsulation is only partial the similarity of structure of the tumor and the adjacent tissue may be very striking.



FIG. 395.—Pericanalicular fibroadenoma. The ducts are surrounded by the new fibrous tissue.  $\times 200$ .



FIG. 396.—Duct papilloma of the breast. The duct is greatly distended by a raspberry-like mass.  $\times 10$ .

The *pericanalicular fibroadenoma* is a much harder tumor, and seldom becomes as large as the preceding variety. It is well encapsulated, and when the sheath is incised it can usually be shelled out quite readily. It has a characteristic mobility when palpated. The cut surface is white, dry, and homogeneous. *Microscopically* there is a proliferation of glandular and fibrous tissue. The new connective tissue surrounds the ducts without invaginating them, hence the name pericanalicular (Fig. 395). The picture suggests less active growth than that of the preceding variety.

The distinction between the two forms, however, is not fundamental. Examine the intracanalicular type and many areas of pericanalicular for-



mation will be found. Taking the broader view we may say that a fibroadenoma may be predominantly intracanalicular or pericanalicular in type. The recognition of the two forms is customary but somewhat unnecessary.

**Duct Papilloma.**—This condition is also known as adenocystoma, papillary cystoma, intracystic papilloma, and many other names. The papilloma projects into a dilated duct, usually in the vicinity of the nipple. At first it is composed of a series of folds so that it resembles a small raspberry, but as it increases in size the folds or villi adhere together so that the surface becomes smoother. Finally it distends the duct and becomes a solid compact mass. *Microscopically* the tumor consists at first of numerous delicate villi covered by epithelium, but as it increases in size and the processes are pressed together, adhere and interlace, gland-like spaces are formed so that the appearance becomes adenomatous (Fig. 396). This explains the use of such a term as adenocystoma. The blood vessels are numerous and thin-walled so that hemorrhage is common, and a blood-stained discharge from the nipple is one of the characteristic symptoms. In some cases a malignant change develops and the condition becomes a duct carcinoma.

### CARCINOMA OF THE BREAST

Cancer of the female breast is one of the commonest forms of malignant disease. It usually occurs during the involution period, *i.e.*, in the years before the menopause, and is rare before the age of thirty-five years. There is a higher incidence in nulliparæ, and the disease bears no relation to repeated suckling. Pregnancy indeed appears to have a protective influence.

**ETIOLOGY.**—Three factors which are of importance in the experimental animal and perhaps also in the human subject are inadequate drainage of the duct system with stagnation and retention of irritating material (Adair and others), irregular or abnormal ovarian stimulation (Lacassagne and others), and some maternal influence transmitted with the mother's milk (Bittner). (1) Breast drainage may be interfered with as the result of anomalies of the duct, a plug of desquamated cells in the duct, etc. The breast of the typical spinster has an underdeveloped, small, hard, fibrosed nipple, and we have already seen that cancer is commoner in those who have never borne children. According to Adair only 8.5 per cent of patients with cancer of the breast give a normal nursing history. Baggs has shown that in a strain of mice with a low incidence of cancer of the breast, ligation of the ducts to the nipples on one side of the body half way through pregnancy frequently produced carcinoma. By means of very rapid breeding without accompanying suckling he also produced a high proportion of cancer. After all, the animal with the most overworked mammary gland in the world, namely, the cow, never develops mammary cancer. (2) The effect of ovarian stimulation can be demonstrated experimentally either by injecting ovarian hormones or by removal of the ovaries. Lacassagne has shown that injection of estrin will produce mammary cancer in mice in a high percentage of cases, even in male mice of a low cancer strain. The preliminary changes are epithelial hyperplasia, dilatation of ducts with the

formation of cysts and papillary processes, and round-cell infiltration. Removal of the ovaries in very young mice with a natural high incidence of mammary cancer will prevent the development of cancer in the inactive breasts. Bilateral carcinoma of the breast in the male has been reported following prolonged estrogen therapy for carcinoma of the urinary bladder. It is evident that estrin can act as a carcinogenic agent. (3) The importance of heredity in the etiology of cancer is well recognized, but Bittner has shown that in mouse mammary cancer some extrachromosomal influence may be transmitted in the mother's milk. If the young of a high breast tumor stock are suckled by mothers of a low breast tumor stock the incidence of breast cancer is greatly reduced. Bittner has succeeded in extracting the cancer-producing factor in the breast of animals with high spontaneous carcinoma of the breast. When this factor was given to animals with a normal incidence of this tumor the incidence rose from 1 per cent to 67 per cent. It seems most probable that the carcinogenic factor is a filterable virus. It is rather startling to learn that the factor may be transmitted by the male mouse as well as by the female. Wood and Darling report a cancer family in which a number of instances of bilateral mammary carcinoma occurred in the course of four generations. In the third generation three sisters developed breast cancer. The cancer occurred only in those women who had been nursed by their mothers, a fact suggesting the operation of a factor similar to the "milk influence" demonstrated by Bittner in mice.

Infiltrating carcinoma may originate *de novo* from normal breast tissue. In many cases, however, there is a preliminary epithelial hyperplasia followed by neoplasia within the ducts before infiltration occurs. This may affect many groups of cells, so that the tumor may be of multicentric origin (Muir), an illustration of wide field of origin of carcinoma. Greene has observed a similar process in rabbits in whom, by means of repeated biopsies, he was able to watch the gradual evolution of the tumor.

Trauma and external irritation bear no relation to cancer of the breast. If trauma were a factor, the disease would be more frequent among the laboring and agricultural classes. That a physical trauma should produce breast cancer is contrary to the dictum that the stimulus to cancer must be of the same type as that to which the particular tissue is biologically best adapted to respond with proliferation.

A great variety of forms of breast carcinoma have been described. Some of the names apply to the gross appearance, some to the microscopic structure, and some to the clinical behavior. The great majority of cases can be placed in one of the following five groups: (1) scirrhus carcinoma, (2) medullary carcinoma, (3) adenocarcinoma, (4) duct carcinoma, and (5) Paget's disease. Rarely the tumor is so undifferentiated that it cannot be placed in any of these groups; this may be called the anaplastic form.

**Scirrhus Carcinoma.**—This is much the commonest form of cancer of the breast. It usually begins in the upper and outer quadrant of the breast, where it forms a hard nodule which can best be appreciated with the palm of the hand. It becomes fixed to the deep fascia and later to the skin, but if the growth occurs midway between fascia and skin the tumor may be freely movable for some time. There may be slight dimpling of the skin

due to lymphatic edema. Fixation and retraction of the nipple is a late symptom, caused by involvement of the large milk ducts. The breast is small and flattened. It must be understood that in the early (operable) stage the only sign may be a hard nodule in the breast. Any such nodule in the breast of a woman in the cancer period may be carcinoma, and should at once be examined. Scirrhus carcinoma grows more slowly than the medullary form, but the ultimate prognosis is no better, because though local growth is slow, dissemination occurs early.



FIG. 397.—Scirrhus carcinoma of the breast. The tumor is in the center of the specimen. It is fairly well circumscribed and depressed below the surrounding tissue; the cut surface is marked by streaks.



FIG. 398.—Carcinoma of breast arising from wall of duct.  $\times 145$ .

The lesion is definitely circumscribed in comparison with cystic hyperplasia, although of course it is not encapsulated and sends processes into the surrounding tissue. It forms a definite *tumor*; an absolutely diffuse lesion is almost certain to be cystic hyperplasia, not carcinoma. It is peculiarly hard, a feature from which it derives its name (*skirros*, hard). It cuts with the grittiness of an unripe pear, so that a diagnosis can often be made the moment the knife enters the tumor. The cut surface is gray, and is seldom homogeneous, presenting yellow or gray streaks which represent clumps of necrotic fatty tumor cells (Plate XXI). The cut surface is concave, retracting below the general level (Fig. 397). Small cysts may be present. The gross appearance of a scirrhus cancer is usually so characteristic that the surgeon is able (or ought to be able) to make his own diagnosis at operation without the assistance of a pathologist. When the tumor is

## PLATE XXI



**Carcinoma of Breast**

The concave surface, the indrawn nipple, the infiltration, and the yellowish-grey streaks are all shown.

exposed it is incised. This is not attended by any danger of dissemination as used to be feared. If the tumor is found to be malignant, radical removal of the breast and the surrounding structures is done at once, whereas if it appears to be benign the entire lump is removed and the diagnosis verified by frozen section on the spot or later paraffin sections. Prior to operation no surgeon in the world can be certain that a localized lump in the breast is not a carcinoma, however innocent it may appear to be.



FIG. 399.—Scirrhous carcinoma of the breast. The compressed groups of tumor cells are separated by a dense stroma.  $\times 175$ .



FIG. 400.—Medullary carcinoma of the breast. The cells are massed together with no stroma between them.  $\times 250$ .

The *microscopic appearance* is also readily recognized. The tumor originates from the epithelium lining a duct (Fig. 398), so that in reality the tumor is a variant of adenocarcinoma, but soon the normal glandular structure becomes replaced by tumor growth, consisting of masses of epithelial cells separated by a dense and abundant fibrous stroma (Fig. 399). This may be so dense that the cancer cells are only present in single file, lying within lymph spaces, and in places they may have disappeared completely. The cells are polygonal and distorted by the dense fibrous tissue; they are small and stain darkly, and mitotic figures are rare. Round-cell infiltration may be present in places.

**Medullary Carcinoma.**—This is merely a variant of the preceding form in which the tumor cells are more numerous and the stroma less abundant. It is, therefore, a soft, rapidly growing, bulky tumor which ulcerates the skin. The cells are grouped in large masses and show numerous mitotic figures (Fig. 400).

*Acute carcinoma* is of the medullary type, although usually more diffuse. It generally develops during lactation, and there is rapid dissemination throughout the breast and skin. It is easily mistaken for the acute mastitis which may complicate lactation, for the breast is hot, swollen, painful, and tender, and there is often a well-marked leucocytosis. The course is very acute and seldom lasts more than a few months.

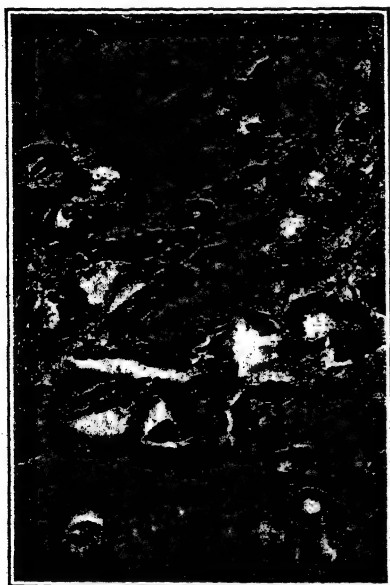


FIG. 401.—Adenocarcinoma of breast.  
× 125.



FIG. 402.—Intraduct carcinoma. The duct is packed with proliferating epithelial cells, but invasion has not yet taken place. × 50.

**Adenocarcinoma.**—This is a rare tumor of the breast in its fully differentiated form. It is of soft consistence and may become quite bulky, but it is of slow growth, of rather low malignancy and may remain localized for a long time. The microscopic appearance is that of gland spaces surrounded by columnar epithelium (Fig. 401).

**Papillary Carcinoma of Duct.**—This tumor usually arises from one of the large ducts near the nipple, and is commonly called duct carcinoma. The growth may originate from duct papilloma. Owing to fusion of the papillary processes a gland-like condition may be produced, so that the lesion has been called cystadenocarcinoma. The tumor is only slowly invasive. Bleeding from the nipple is a common symptom.

*Intraduct carcinoma* is a convenient term applied to those cases of cystic hyperplasia in which a malignant change is added to epithelial hyper-

plasia, but the tumor cells are still confined within the walls of the ducts (Fig. 402). Such a condition tends to be diffuse in contrast to papillary carcinoma of the main ducts which is a localized lesion. It may be very difficult for the pathologist to decide before invasion has occurred whether such a specimen is malignant or not. The "comedo carcinoma" of Bloodgood (so called because worm-like casts can be expressed from the cut surface) belongs to this group.

**Paget's Disease.**—The condition described by Sir James Paget in 1874, and since known as Paget's disease of the nipple, is a chronic eczema of the nipple with the development after some years (sometimes as long as ten



FIG. 403.—Paget's disease of the breast showing clear Paget's cells in the hypertrophic epidermis.  $\times 325$ .

years) of a cancer in the breast. In the past there has been much difference of opinion as to whether the skin condition or the cancer was the primary lesion. The skin lesion is malignant, but of very slow growth and without glandular involvement. The breast tumor may be of rapid growth. The eczematous area at the nipple is usually bright red and either moist and weeping or dry and scaly. *Microscopically* the skin in the affected area shows marked epidermal hypertrophy before ulceration takes place. The most characteristic feature is the presence of the peculiar structures known as Paget's cells (Fig. 403). These are large, clear, vacuolated cells with small pyknotic nuclei. They look like clear spaces punched out of the epidermis. They are most abundant in the basal layers, but may permeate the entire thickness of the epidermis. The underlying dermis shows infiltration with lymphocytes and plasma cells. In the later stages there is ulceration of the epidermis.

The pathogenesis of the condition is still a matter of dispute. Muir and others believe that it begins as an intraduct carcinoma, and that the cancer cells spread along the duct and penetrate between the cells of the epidermis (intraepithelial spread of carcinoma). Frequently the tumor appears to begin as a local lesion at or near the outlet of a lactiferous duct, whence it spreads centrifugally both in the duct epithelium and in the epidermis, but the continuity is broken when some parts die while others remain alive, so that there may be no connection between the epidermal lesion and the tumor in the breast (Inglis). In such cases Cheatele suggests that the carcinogenic agent has acted both on the epidermis and on the breast tissue at a distance, a view with which the writer is in agreement. In support of this is the fact that a series of ducts may show neoplastic change.

In rare instances the lesion has occurred outside the breast. Paget himself described such a case. The tumor is usually in the region of the anus, and may or may not be associated with carcinoma of the rectum.

**Spread of Breast Carcinoma.**—The cancer cells are spread by infiltration, by the lymph stream, and by the blood stream.

*Infiltration* is the means by which the malignant cells spread throughout the breast. They infiltrate the tissue spaces between the fat cells and connective-tissue bundles, as can be best seen in the scirrhus form of cancer. It is in this way that the deep fascia and skin are involved. Adenocarcinoma and duct carcinoma show a comparatively slight tendency to infiltration. Microscopic sections of the whole thickness of the breast show that the pectoral muscle is involved in over one-half the cases of scirrhus carcinoma at the time of operation, although no gross evidence of involvement may be apparent. This indicates the need of wide removal of the tissues underlying the breast.

*Lymphatic spread* carries the tumor cells to a distance. There are two ways in which this spread may occur. The cells may grow along the lymphatics by a process originally described by Sampson Handley and named by him lymphatic permeation. Or they may be carried by the lymph stream in the form of tumor emboli. It appears probable that embolism is a much more important method than permeation, although for a long time it was thought that permeation was the chief method of spread. The tumor cells reach the axillary lymph nodes early in the disease, especially in the scirrhus form of carcinoma. These nodes show *microscopic* involvement in over 60 per cent of cases at the time of operation. The mediastinal nodes may occasionally be involved quite early, sometimes even before the axillary nodes. It is in these cases that surgery is so helpless. Adenocarcinoma and duct carcinoma rarely invade the nodes, but unfortunately these are uncommon forms of cancer of the breast. R. S. Handley points out that the internal mammary lymphatic chain may be involved without invasion of the axillary nodes. This may explain why early cases of carcinoma of the breast show a recurrence of about 25 per cent within five years of radical mastectomy.

Enlargement of the regional lymph nodes may be due not to metastases but to hyperplasia of histiocytes which fill and distend the sinusoids, a sinus histiocytosis, which when present in high grade indicates a favorable prognosis (Black *et al.*). A similar change is seen in the follicles. A



high grade of sinus histiocytosis, regardless of metastases to the nodes, is usually associated with a survival period of five years or more. Conversely, absence of histiocytosis, even though no cancer cells can be found in the nodes, is likely to be associated with recurrence within five years of operation.

The plexus of lymphatics which lies upon the deep fascia becomes filled with tumor cells, and it is along the planes of the deep fascia and the muscular aponeuroses that the principal spread takes place. The nodules which often appear in the skin after removal of the tumor owe their origin to this deep supply of tumor cells. Obliteration of the deep lymphatics may cause a lymphatic edema of the skin, and as the epidermis is anchored at many points by hair follicles, the intervening skin becomes swollen so as to give a characteristic dimpled appearance known as *pig skin* or *peau d'orange*. The condition spoken of as *cancer en cuirasse* is due to lymphatic edema rather than to invasion of the skin by tumor cells. The pleural and peritoneal cavities may be invaded by lymphatic spread along the fascial and aponeurotic planes. The lung may be invaded from the bronchial lymph nodes, and the liver by way of the lymphatics in the falciform ligament.

*Blood spread* leads to involvement of distant organs. Gentle palpation prevents a tumor thrombus in a vein becoming an embolus. Rough handling of the breast is much more dangerous than biopsy. Metastases occur most frequently in the lungs and liver, the next most common locations being the adrenals, spleen and ovaries (Saphir and Morris). It is in the red marrow that the tumor cells lodge, so that metastases are found in the vertebræ, the flat bones, and the proximal ends of the humerus and femur. Spread by the vertebral set of veins is probably responsible for involvement of the vertebræ and the skull.

**PROGNOSIS.**—In estimating the prognosis in cancer of the breast, clinical features are of greater value than the microscopic appearance. At the same time we may recognize that the scirrhus and medullary types have a worse prognosis than adenocarcinoma, duct carcinoma, and Paget's disease. The younger the patient and the more rapid the growth, the worse the outlook. Lymph node involvement is the most important factor, as it is an index to the degree of spread. Reference has already been made to the relation which a histiocytic reaction in the nodes may have to the prognosis. It is difficult to be certain if a patient has been cured, for the disease may recur after a number of years in the mediastinal lymph nodes. The average duration of life in untreated cases is three years. Of patients treated by the radical operation, 50 per cent are alive and well after three years and 30 per cent after ten years. Of patients in whom the disease is still confined to the breast, over 85 per cent are alive and well at the end of ten years. These figures are taken from the report of Janet Lane-Clayton to the British Ministry of Health, based on a most exhaustive investigation.

**EFFECT OF RADIATION.**—The radio-sensitivity of cancer of the breast varies markedly with the type of growth. About 20 per cent of the cases are radio-sensitive, 20 per cent are resistant, and 60 per cent are intermediate. Unfortunately radio-sensitivity is no criterion of certain cure. The more sensitive the tumor, the more cellular it must be, and the more cellular the more dangerous on account of the earlier formation of metastases. Scirrhus carcinoma, as might be expected, is highly radio-resistant. The medullary form, on the other hand, may be quite radio-sensitive. Adenocarcinoma and duct carcinoma do not respond well to

radiation. The rapidly growing anaplastic forms respond best, but have the worst prognosis.

*Carcinoma of the male breast* is rare. It is usually of a rather high grade of malignancy.

**SARCOMA.**—This is also uncommon. It may attain a great size. The cut surface presents a characteristic homogeneous appearance like fish-flesh, and shows none of the yellow necrotic areas and striations characteristic of carcinoma. This, combined with its softness, usually allows a correct diagnosis of the tumor to be made with the naked eye. The sarcoma may develop from a fibroadenoma, in which case it is composed of spindle cells arranged around ducts. In the ordinary form which arises *de novo* it is made up entirely of spindle cells, many of which show mitotic figures. The lymph nodes are seldom involved, but there may be distant blood spread.

*Other tumors* which may rarely be found in the breast are angioma, lipoma, myxoma, osteogenic sarcoma, and chondroma.

**BLEEDING FROM THE NIPPLE.**—The two common causes of discharge of blood or blood-stained fluid from the nipple are duct papilloma and duct carcinoma. There is much difference of opinion as to whether or not the symptom usually indicates malignancy; but it seems probable that about 50 per cent of the cases are benign and 50 per cent are malignant (Adair). It is important to realize that the discharge may not contain blood although the patient says that it does, and in every case a microscopic examination should be made of a smear. Cystic hyperplasia may cause a discharge from the nipple which is chocolate, green, or yellow in color, but which contains no blood. A dark, stagnant, bloody discharge is practically pathognomonic of duct carcinoma. Transillumination of the breast is useful for localizing the lesion, for a collection of blood appears black with this method.

## CYSTS OF THE BREAST

The common cysts of the breast are those of cystic disease. These are not retention cysts due to obstruction of the ducts, but are first produced by dilatation from epithelial hyperplasia, followed by incomplete involution which leaves the duct dilated. Obstruction may then be superadded, so that continued secretion may lead to a great increase in size. A feature of these cysts is that the clear fluid which they contain may be under marked tension, so that it spurts out violently when the cyst is incised. A *galactocele* is a very rare condition in which a large cyst containing milk is formed during lactation. Being a dilatation of one of the main milk ducts, it is situated close to the nipple. *Hydatid cysts* are extremely rare.

## ACUTE MASTITIS

Acute inflammation of the breast is practically confined to the first few weeks of lactation. Physiological hyperplasia may occur immediately after birth and at puberty, and when unduly marked this may cause symptoms which are described clinically as acute mastitis, but it is not a true inflammation. The common infecting organism is the *Staphylococcus aureus*, which produces a localized inflammation. More rarely a streptococcus may cause a diffuse inflammation. Infection takes place through the milk ducts or cracks in the nipple. Suppuration occurs and an abscess may be formed. This may be subcutaneous, intramammary, or retromammary. In the latter form the breast is pushed forward. Only one segment of the breast may be involved, or a number of abscesses may be formed in adjoining lobes so that multiple incisions are required. Acute mastitis may be closely simu-

lated by acute carcinoma, a condition characterized by pain, swelling, heat, and fever.

## OTHER LESIONS OF THE BREAST

**FAT NECROSIS.**—It has long been known that a quiet necrosis with saponification may occur in traumatized or ischemic fat in any part of the body, a process similar to pancreatic fat necrosis but of slower *tempo* due to absence of the active pancreatic lipase. Within recent years it has been recognized that such a process in the breast may give rise to a lesion which closely simulates scirrhus carcinoma (Lee and Adair). A history of trauma to the breast shortly before the appearance of the lesion is obtained in many cases, so that the condition is commonly called traumatic fat necrosis, but in about one-half the cases there is no such history. The patients are usually corpulent with large full breasts, and most cases occur in the fourth and fifth decades. A hard localized mass is formed, which is often adherent to the skin, so that the condition is readily mistaken for cancer.

The *gross appearance* of the lesion is characteristic, and should be recognized in the operating room. The affected area is of an opaque, white, chalky appearance, which is well shown in one of Hadfield's illustrations. This area is composed of necrotic fat. As saponification proceeds liquefaction takes place, and a cavity is formed containing a pool of yellow oily fluid. This pseudocyst is surrounded by dense tissue which represents a reaction to the fatty irritant. Lime salts combine with the liberated fatty acids, so that some degree of calcification is common. The cicatricial contraction, the concave surface, and the yellow streaks of scirrhus carcinoma are absent.

The *microscopic appearance* is similar to that of fat necrosis elsewhere in the body. The fat cells are broken into droplets which remain attached to the cell envelope and stain faintly with hematoxylin. Fatty acid crystals may be present. The surrounding tissue shows a chronic productive inflammation, and contains large numbers of phagocytic cells filled with lipid material. Foreign body giant cells form a striking feature of the lesion. Lymphocytic infiltration and an obliterating endarteritis complete the picture.

**PLASMA CELL MASTITIS.**—This rare condition is an acute or subacute inflammation which begins suddenly with pain, tenderness, diffuse swelling, and enlargement of the axillary lymph nodes. The acute symptoms soon subside, leaving the breast hard, the skin adherent, and the lymph nodes firm, so that to mistake it at this stage for carcinoma is almost inevitable. The gross appearance is that of a hard diffuse mass, so that again there is resemblance to carcinoma. The microscopic appearance is explained by the pathogenesis. The condition is an inflammation initiated by stasis and inspissation of secretions with rupture of the mammary ducts, often associated with a history of difficult nursing. It is an endogenous granuloma, and has been called spilt milk mastitis. The lesion, which may resemble tuberculosis but without caseation, consists of large numbers of plasma cells, together with varying numbers of polymorphonuclears, epithelioid cells, foam cells and giant cells which may be clustered around fatty acid crystals. A developing fibrosis increases the induration.

**TUBERCULOSIS.**—Tuberculosis of the breast is uncommon but not rare. At first it takes the form of a hard mass, which is easily mistaken for carcinoma. Softening occurs, with the formation of large tuberculous cavities and sinuses opening on the surface. The microscopic picture is characteristic of tuberculosis.

**ACTINOMYCOSIS.**—This is one of the rarest of breast diseases. It may involve the breast by extension through the chest wall from the pleura.

**HYPERTROPHY.**—Hypertrophy of the breasts usually comes on soon after puberty, but may occur during pregnancy or lactation. It is probably of endocrine origin.

due to some abnormal action of the ovarian hormone. The hypertrophy involves both glandular and connective tissue, but as a rule most of the enlargement is due to a great increase of the connective tissue, which is soft and of open structure.

**CONGENITAL ANOMALIES.**—*Amastia* or congenital absence of the breast is usually bilateral but may be unilateral. *Athelia* or absence of the nipple is rare. It may be associated with *amastia*, or the breast may be well developed. *Polymastia* or abnormal number of breasts is much more common than either of the preceding conditions. The "milk-line" extends from the axilla to the groin, and accessory or supernumerary breasts may occur anywhere along this line, the most common site being the axilla. The accessory mammary tissue may or may not be provided with a nipple. The mass enlarges during lactation and may secrete milk. *Polythelia* or accessory nipples are rare. They may occur on the breast or elsewhere along the milk-line. In the latter case they have underlying mammary tissue (*polymastia*).

#### ADDITIONAL READING

- Carcinoma.** ADAIR: New York State J. Med., 1934, 34, 61. BAGG: J. Cancer Research, 1925, 9, 498. BITTNER: Am. J. Cancer, 1937, 30, 530; 1939, 35, 90. GREENE: J. Exper. Med., 1939, 70, 147, 159 and 167. HANDLEY: Cancer of the Breast, 2nd ed., London, 1922. HANDLEY AND THACKRAY: Lancet, 1949, 2, 276. LACASSAGNE: Compt. rend. Soc. de biol., 1934, 116, 844. MUIR: J. Path. and Bact., 1941, 52, 155. WOOD AND DARLING: Cancer Research, 1943, 3, 509.
- Cystic Hyperplasia.** BUNTING: Bull. Internat. Ass. Med. Museums, 1948, 28, 48. LENDRUM: J. Path. and Bact., 1945, 57, 267. RODMAN: Arch. Surg., 1930, 20, 515. ROSENBERG: Frankfurt. Ztschr. f. Path., 1922, 27, 466. SMITH: Canad. M. A. J., 1940, 43, 70.
- Fat Necrosis.** HADFIELD: Brit. J. Surg., 1929, 17, 673.
- General References.** GESCHICKTER: Diseases of the Breast, Philadelphia, 1945.
- Histological Variations.** INGLEBY: Arch. Path., 1942, 33, 573.
- Lymphnodes in Carcinoma.** BLACK *et al.*: Am. J. Path., 1953, 29, 505.
- Paget's Disease.** DUNN: J. Path. and Bact., 1930, 33, 297. INGLIS: Paget's Disease of the Nipple, London, 1936. MUIR: J. Path. and Bact., 1927, 30, 451; 1939, 49, 299.
- Plasma Cell Mastitis.** ADAIR: Arch. Surg., 1933, 26, 735. CROMAR AND DOCKERTY: Proc. Staff Meet., Mayo Clinic, 1941, 16, 775. RODMAN AND INGLEBY: Ann. Surg., 1939, 109, 921.
- Relation of Cystic Hyperplasia to Carcinoma.** BLOODGOOD: Arch. Surg., 1921, 3, 445. CAMPBELL: Arch. Surg., 1934, 28, 1001. CHARTERIS: J. Path. and Bact., 1930, 33, 101. KEYNES: Lancet, 1923, 2, 439. TAYLOR: Arch. Surg., 1930, 21, 412. WARREN: Surg., Gynec. and Obst., 1940, 71, 257.
- Spread of Carcinoma.** FITZWILLIAMS: Brit. J. Surg., 1925, 12, 650. SAPHIE AND PARKER: Arch. Surg., 1941, 42, 1003. WAINWRIGHT: Surg., Gynec. and Obst., 1931, 52, 549. WARREN AND WITHAM: Surg., Gynec. and Obst., 1933, 57, 81.
- Sweat Gland Carcinoma.** DAWSON: Edinburgh Med. J., 1932, 39, 409.

## Chapter

## 28

### THE DUCTLESS GLANDS

IN THIS chapter the diseases of the ductless glands will be considered. There are no organs in the body in which it is so difficult to correlate changes in function with changes in structure as the members of the endocrine system, for the reason that our knowledge of their function is still so meager and vague. We shall therefore have to be content with describing the lesions found in disease and the disturbances produced by altered function without much attempt at correlating the two. The ductless glands are the chemical regulators of the body by virtue of the hormones (*hormao*, to excite) which they produce. The hormones govern the processes concerned with growth, metabolism, and reproduction. Of special importance in pathology is the fact that some of the hormones control the metabolism of certain inorganic elements, and that upset of this control may have serious effects. Thus the adrenal cortex controls sodium metabolism, the thyroid iodine metabolism, and the parathyroids the metabolism of calcium and phosphorus.

**Interrelationships.**—The ductless glands are members of the endocrine system, but they are also "members one of another," for at least some of them exert an important influence upon other members of the series. It would indeed be rash for a mere pathologist to venture forth on the uncharted sea of the endocrines, strewn as it is with the wrecks of shattered hypotheses, where even the most wary mariner may easily lose his way as he seeks to steer his bark amid the glandular temptations whose siren voices have proved the downfall of many who have gone before. And yet the fact that the ductless glands do form an interrelated system cannot be passed over in silence. The anterior lobe of the pituitary exerts a profound influence on the adrenal cortex, thyroid, ovary and islets of Langerhans, and this influence is to some extent reciprocal. If one ductless gland influences another it may be either in the direction of stimulation or inhibition. If this influence becomes exaggerated, the resulting effect will be of a mixed type due to excess or deficiency in the internal secretion of two members of the series. In this way the so-called polyglandular syndromes may arise.

The relation of the anterior lobe of the pituitary to the ovary has already been discussed in connection with gynecological pathology, and will be referred to again later in this chapter. It affords an example of a physiological relationship under normal conditions (action of anterior pituitary on ovary) and of a pathological relationship (Fröhlich's syndrome or failure of sexual development in pituitary disease). The adrenal cortex has a

marked influence on the gonads; some tumors of the adrenal cortex are associated with premature sexual development in boys and virilism in the female. The adrenal seems to be concerned with the male side of development and the pituitary with the female side. It appears that with respect to endocrine organization the female is essentially a hermaphrodite in whom the masculine component is never extinguished but merely quiescent. For this reason virilism in the female is always more striking than femininity in the male.

### ADDITIONAL READING

**General References.** SOFFER: Diseases of the Endocrine Glands, Philadelphia, 1951.

## THE ADRENALS

**DESCRIPTIVE OUTLINE.**—The right adrenal is triangular like a cocked hat, the left is crescentic. The weight is 5 to 6 grams. The cut surface shows cortex and medulla. The cortex is much more abundant; indeed in many sections no medulla can be seen. The outer part of the cortex is light yellow owing to the abundant lipids it contains, the inner part (*zona reticularis*) is dark brown and often shows softening or cavitation at autopsy. A very common error is to mistake this inner layer for the medulla, especially when there happens to be no medulla in the slice inspected. The medullary tissue is white or gray, and may sometimes be seen adhering to the wall of a cavity in the *zona reticularis*. It is stained brown by immersion in a solution of a chrome salt (*chromaffin reaction*).

The *development* of the adrenals presents some curious features. In fetal life the adrenal is almost all cortex, and at the third month it is actually larger than the kidney. Unlike the cortex after birth the fetal cortex contains no lipids. The rate of weight compared with that of the kidney is 1 to 3.5, whereas in the adult it is only 1 to 30. Immediately after birth a strange change takes place. The entire fetal cortex rapidly degenerates and is slowly replaced by adult cortex and medulla, but it is not until the twelfth year that the original size of the adrenal at birth is regained. Massive hemorrhage may occur into the degenerating cortex at birth, and as the hemorrhage is often bilateral it may prove fatal to the child. In the *anencephalic fetus* the cortex is absent, so that the adrenals are very atrophic. This maldevelopment of the adrenals is probably the result of interference with the development of the pituitary, for the posterior lobe of the pituitary is often missing (*Angvine*). Accessory cortical tissue is common at birth, but it soon atrophies and disappears. Occasionally it persists into adult life as small bright yellow nodules which are found under the capsule of the liver and in the line of descent of the gonads, *i.e.*, in the kidney, along the spermatic vein, in the broad ligament, testicle and ovary.

**PATHOLOGICAL PHYSIOLOGY.**—This is no place to explore the almost pathless labyrinth of adrenal physiology, but a brief consideration of a few established principles is necessary if the student is to appreciate the pathological pictures which disturbances of cortical function may produce. It is well to remember that any such statement is apt to be out of date before it appears in print.

It is just over 100 years since Addison opened the door and allowed us our first peep into the working of the adrenals. He observed that patients with adrenal insufficiency often died from minor infections and stresses. We now know that it is the adrenal which enables the body to withstand the large variety of environmental stresses and strains to which it is subjected. The adrenal plays perhaps the largest

single rôle in determining whether any person is sick or well. Removal or destruction of the cortex of both adrenals is invariably followed by death. The adrenals are more essential to life than is the pituitary. The result of removal of the adrenals is increase in the urinary excretion of sodium, accompanied by marked loss of water, reduction in the circulating plasma volume, and eventually dehydration and shock. There is a corresponding though less marked increase in the excretion of chloride, but a decreased excretion of potassium which accordingly accumulates in the serum. These changes seem to be due to loss of control of the permeability of membranes. Renal failure may develop as the result of the dehydration and shock caused by the loss of salt and water. A similar clinical picture develops as the result of chronic adrenal insufficiency in Addison's disease. Hypoglycemia may also occur. In both the experimental animal and in the patient the entire picture can be reversed by the administration of adrenal cortical hormone.

More than 20 chemically distinct steroids with varying degrees of physiological action have been isolated from the adrenal cortex. They may be divided into three groups, which regulate three broad types of body activity: electrolyte balance; carbohydrate, protein, and fat metabolism; and androgenic and anabolic function. This grouping, which is the golden thread to guide the hapless wayfarer through the labyrinth, may be referred to colloquially, though not academically, as the salt, sugar and sex hormones.

(1) The *salt or electrolyte group*, the mineralocorticoids of Selye, of which the principal example is synthetic desoxycorticosterone, governs sodium and chloride retention and potassium excretion, and therefore the volume of plasma and extracellular fluid. Administration of the hormone in excess leads to edema and increase of body weight due to retention of sodium and chloride, to fatigue and electrocardiographic changes due to potassium depletion. It is essential to life. Deficiency of this group results in the picture of Addison's disease and leads to death. Excessive quantities produce the picture of hypertension in experimental animals (Selye).

(2) The *sugar or S group*, the glucocorticoids of Selye, is characterized by the presence of the all-important oxygen at the  $C_{11}$  position. Hormones of this type are gluconeogenic, i.e., they convert amino acids into sugar instead of into protein, increasing blood sugar and liver glycogen. In this sense they may be regarded as antianabolic. They cause lysis of lymphocytes, both those in the blood and those in the lymph nodes, and circulating eosinophils are almost completely eliminated. In excess they produce the picture of Cushing's disease, while deficiency is associated with the lesions seen in Selye's alarm reaction in experimental animals, and possibly to the collagen diseases. The best known example of this group is cortisone (17-hydroxy-11-dehydrocorticosterone).

Cortisone, in addition to influencing protein, carbohydrate and fat metabolism, seems to act on the intercellular substance and to affect the permeability of cell membranes. It also interferes with the antigen-antibody response, and it inhibits the formation of antibodies due probably to the rapid atrophy of lymphoid tissue which it induces. Cortisone suppresses the inflammatory response of the tissues to practically all forms of irritation, so that it eliminates the natural barriers to infection. In experimental infections the microorganisms grow unrestrained, a fulminating bacteremia develops, and the animals remain active and happy until they die. In other words, cortisone relieves the symptoms of disease without influencing the cause. Although it may be dangerous in infections, its greatest use is in those non-bacterial inflammations which are grouped as the collagen diseases. If the inflammation is short-lived, as in rheumatic fever, cortisone may be of great value, but in long-continued inflammation such as periarteritis nodosa and disseminated lupus, when the hormone is withdrawn the inflammation starts up again. As Hench, the discoverer of the clinical use of cortisone, puts it in his Nobel lecture,

the hormone acts as an asbestos suit behind which the patient protects his tissues from the fire. It does not put out the fire nor does it repair the fire damage. Indeed very large doses in certain species prevent the formation of granulation tissue and inhibit fibroblastic proliferation, but in clinical therapeutic doses it does not interfere with the healing of clean wounds. On the other hand perforation of a peptic ulcer seems to be commoner in patients on prolonged cortisone therapy.

(3) The *sex group*, usually known as the *nitrogen* or *N* group, governs androgenic and anabolic functions. These hormones masculinize the body, and increase the synthesis of amino-acids and protein from nitrogen. As they are anabolic in effect they tend to counteract the action of the previous group. They favor retention of nitrogen, phosphorus, potassium, sodium, and chloride. These steroids when metabolized possess a ketone group on the 17th carbon atom. They are usually excreted in the urine, where they provide a valuable index of the activity of the adrenal cortex and the testes. The urinary excretion of 17-ketosteroids is greatly increased in tumors and hyperplasia of the cortex, in virilism, and in Cushing's syndrome. It is extremely low in Addison's disease and in Simmonds' disease, the latter caused by destruction of the anterior pituitary.

*Pituitary-Adrenal Relationship.*—That the adrenal cortex is stimulated by the anterior pituitary has been known for many years. Hypophysectomy leads to atrophy of the adrenal cortex, whilst the administration of ACTH causes a marked increase in the size and activity of that structure. This relationship is a reciprocal one, for both atrophy and hypertrophy of the adrenal cortex lead to structural changes in the anterior pituitary. It would now appear that the pituitary may secrete more than one adrenocorticotrophic factor, and that each group of adrenal cortical hormones has its own tropic pituitary analogue. A simple anterior pituitary extract (L.A.P. of Selye) stimulates the production of the group 1 hormones, whilst ACTH stimulates the group 2 and possibly the group 3 hormones. It is probable that ACTH is produced by the basophils of the pituitary. An intact adrenal cortex is necessary for an adequate response. Prolonged administration of ACTH will lead to adrenal hyperplasia, whereas similar use of cortisone will result in atrophy both of the adrenal and the anterior pituitary.

The hypothalamus is an essential link in pituitary-adrenal activation. Epinephrine and various forms of stress can stimulate hypothalamic centers to secrete a humoral substance that excites production of ACTH. Subcutaneous injection of epinephrine reduces the eosinophils 50 per cent or more. The pituitary is evidently under the influence of hormones not only of the adrenal cortex but also of the medulla.

*Stress.*—The subject of stress in relation to adrenal and pituitary activation has attained much prominence through the animal experimental work of Selye, and there is a widespread tendency to apply to human disease not only the experimental results but the hypothesis of the "general adaptation syndrome" which has been erected on this work. It is important to keep in mind that effects observed in the rat are not necessarily duplicated in man, and that in the field of the adrenal hormones the response varies markedly in different species.

The idea of *specific* adaptation is, of course, an old one. Every physiological response to a stimulus or "stress" is such an adaptation. In the bacteriological field the production of a specific antibody to a given antigen is a classic example. The part played by the adrenal in the body's adaptation to stress was recognized in Cannon's emergency theory, in which epinephrine was produced by the adrenal medulla in times of anger, combat and flight when the immediate conversion of glycogen into fuel was urgently needed.

Selye's contribution is the idea that in addition to specific adaptation there is a *general* adaptation mechanism or syndrome which helps to raise resistance to stress (infections, trauma, nervous strain, heat, cold, muscular fatigue, and x-radiation)



irrespective of the specific nature of the stimulus. In this mechanism the endocrine system, and in particular the pituitary-adrenal axis, plays an essential part. In the experimental animal the general adaptation syndrome is characterized by enlargement of the adrenal cortex with increased secretion of corticoids, involution of the thymus and lymphoid organs, gastrointestinal ulcers, and certain metabolic changes. If the stress continues, the general adaptation evolves in three stages. (1) The *alarm reaction* or "call to arms" is the result of sudden exposure to stimuli for which the individual is not prepared. Fear, anger, trauma, etc., act on the adrenal medulla by way of the parasympathetic nerves with the production of epinephrine, and the resulting conversion of the glycogen reserve into glucose for the purpose of energy. This is Cannon's emergency mechanism. There then follows ACTH stimulation of the adrenal cortex with the production of corticoids. (2) The *stage of resistance*, that is to say optimal non-specific resistance to prolonged stimuli. (3) The *stage of exhaustion*, in which the general adaptation fails. Examples of the three stages of alarm, resistance and exhaustion are the severely burned man who, after receiving treatment, returns to help put out the fire and dies a day or two later, and the wounded soldier who fights on, seems to do well for a while, and then succumbs to secondary shock.

Selye also suggests a new concept under the title of *diseases of adaptation*, or even better, maladaptation. Some of the most common diseases of man have been included under this heading, i.e., hypertension, nephritis, nephrosclerosis, the rheumatic and other collagen diseases, and ulcerative colitis. These are said to be due to a "derailment" of the defence mechanism. These derailment diseases are manifestations of hypercorticism, the particular target organ (joint, artery, bowel) being determined by such conditioning factors as constitution, diet, etc. The basis for this hypothesis is that the administration of mineralocorticoids (the salt or electrolyte group) such as desoxycorticosterone produce in animals experimental replicas of the rheumatic and hypertensive diseases such as arthritis, periarteritis nodosa, and hyaline necrosis of arterioles. These are relieved by the glucocorticoids (cortisone). The suggestion is that an imbalance between mineralocorticoids and glucocorticoids is the basis for this large group of diseases. In the final analysis the imbalance may be pituitary rather than adrenal, for whilst the output of glucocorticoids is dependent on ACTH, the output of mineralocorticoids seems to depend on STH, the somatotrophic or growth hormone of the pituitary. This may be true in the rat but not in man.

Selye's experimental work and theoretical explanations are of great interest, and have served as a stimulus to much investigation and thinking. In essence the idea of the general adaptation syndrome (which is not a syndrome in the proper use of the word but a mechanism) is that the body reacts to all varieties of stress by pituitary stimulation of the adrenal cortex. Sometimes, for some unknown reason, the cortex reacts by producing an excess or imbalance of mineralocorticoids. This results in a host of ills which have been collected under the umbrella term diseases of adaptation. Now, there is a world of difference between a hypothesis and a principle. As Pickering remarks in this connection: "The history of medicine shows how great is the tendency for a tentative hypothesis to assume the guise of a so-called fundamental principle." The suggestion of excess production of mineralocorticoids is a pure guess, a hypothesis which future work may prove or disprove. The introduction of a number of new names must not be confused with the discovery of new facts. There is a large group of diseases of unknown etiology. Many of these have been attributed in the past to focal infection and more recently to psychosomatic disorder. To now call them diseases of adaptation and attribute them to stress may be an important advance. It must be remembered, however, that in many examples of these diseases there is no evidence of stress, and there are many examples of stress without accompanying disease. It is difficult to under-

stand how diseases having such different incidence, different lesions, and different course can arise from one and the same mechanism. ACTH works wonders in the collagen diseases, but there is no laboratory evidence of altered adrenal function in these diseases, nor proof of increased production of mineralocorticoids. It must not be forgotten, however, that, apart from the estimation of eosinophils in the blood and 17-ketosteroids in the urine, our tests for adrenal cortical function are still only the shadow of a shadow.

Finally it must be remembered that stress is not necessarily harmful. Without stress, as Arnold points out in a thoughtful and stimulating address to which I had the pleasure of listening in Honolulu, plants, animals, men and even civilizations tend to degenerate and wither away. Orchids need comparative drought to produce their best blooms, bones freed from the stress of weight-bearing undergo osteoporosis, a climate with marked variations in temperature is likely to produce a people physically and intellectually superior, and the great civilizations have developed in lands where conditions were hard and life was difficult.

The *cholesterol content* of the cortex varies under pathological conditions (Rogers and Williams). It is low in stress states such as acute infections, burns and trauma, as well as in chronic debilitating diseases, but it is high in cardiovascular and renal disease.

### ADRENAL INSUFFICIENCY. ADDISON'S DISEASE

This disease is of great historical interest, because Addison's demonstration that the syndrome of progressive weakness, pigmentation of the skin, and gastro-intestinal disturbance was due to lesions of the adrenals was the first indication that constitutional disease could be caused by lesions of a ductless gland, and thus formed the starting point of the entire subject of endocrinology.

**SYMPTOMS.**—The characteristic asthenia is gradual in onset, the heart's action is feeble, the blood pressure remarkably low. The gastro-intestinal symptoms are nausea, vomiting, and attacks of diarrhea. The pigmentation, which ranges from light yellow to deep brown, is most marked on exposed parts and in regions where normal pigmentation is well marked (areola of nipples, genitals, etc.). The relation of the adrenal lesions to the pigmentation has already been discussed in connection with the general problem of melanosis on page 33. It seems probable that the adrenal insufficiency leads to compensatory overproduction of MSH, the melanoblast-stimulating hormone of the pituitary which governs the conditions necessary for tyrosinase-tyrosin reaction in the melanoblast with the production of melanin. The mucous membranes of the mouth and vagina are often pigmented. When the patient is put on a chloride-free diet and given potassium there is a large excretion of chlorides in the urine, whereas in a normal person under similar conditions it is quite small. Although the downward course is generally gradual, there may be remissions and exacerbations. The latter are known as *crises*, and are marked by extreme arterial hypotension, decrease in the blood volume, gastro-intestinal symptoms, and shock, sometimes terminating in sudden death. Hypoglycemia is apt to develop, and death may be due to hypoglycemic shock. An important function of the adrenal cortex is regulation of the water and sodium chloride balance, so that in Addison's disease loss of sodium and chloride and water is a striking feature, and many of the symptoms are relieved by the administration of salt. Estimation of chloride excretion in the urine is a valuable test. There is retention of potassium in the blood, probably due to a change in the permeability of cell membranes and consequent disturbance of potassium exchange. The blood

urea is frequently increased, due apparently to failure in renal function caused by fall in glomerular filtration pressure.

**LESIONS.**—The usual lesions of the adrenals (always bilateral) may be of three varieties: tuberculosis, atrophy, and secondary tumors. Of these *tuberculosis* used to be the most common (Fig. 404). It is of the chronic fibrocaceous type. The patient seldom shows clinical evidence of tuberculosis, and it may be difficult to find the primary lesion which is the cause of the infection. Both cortex and medulla are destroyed, but a small portion of cortex always remains, otherwise life could not have been supported. The



FIG. 404.—Addison's disease. Enlargement of the adrenal the result of caseous tuberculosis.

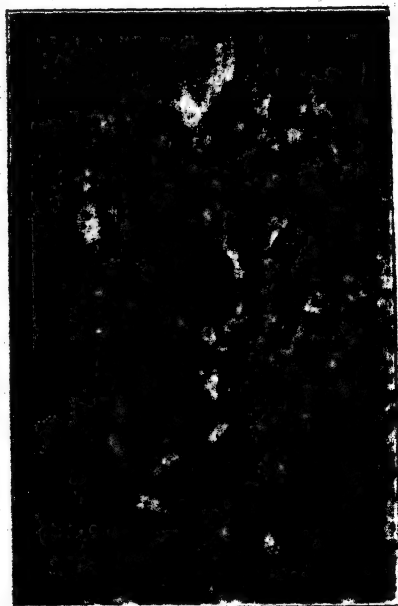


FIG. 405.—Atrophy (necrosis) of the adrenal cortex.  $\times 250$ .

disease is confined to the adrenals and the kidneys are not involved, nor does renal tuberculosis spread to the adrenals and cause Addison's disease.

(2) *Simple atrophy* (so-called) is a necrosis of the adrenals rather than an atrophy, although all trace of the active process may have been lost. It is apparently very much commoner than it used to be. Duffin found necrosis to be the causal factor in 41 per cent of the cases studied in my department. Many of these patients (male) have scanty hair on the face and body, a feature which makes it possible to prophesy that necrotic atrophy will be found in such cases. The adrenal glands are very small, and usually show marked lymphocytic infiltration (Fig. 405). In some

cases only the cortex is affected by the atrophy, the medulla remaining intact. Wells, comparing this necrosis with the acute yellow atrophy of the liver produced by cinchophen and the selective destruction of marrow elements by aminopyrin, etc., resulting in agranulocytosis, suggests that the adrenal atrophy may be due to one of the newer drugs in those who have an idiosyncrasy for it. (3) *Bilateral tumor formation* is a rare cause. The tumor is usually a secondary carcinoma. In rare cases primary carcinoma of the cortex on both sides has given rise to the picture of Addison's disease. Bilateral amyloid disease of the adrenals may also cause the condition.

The pituitary shows changes which are presumably secondary in nature. The chromophobe cells are increased in number, with many exceptionally large examples, the acidophils are slightly reduced, and there is extreme reduction in the number of basophils, many of which are of abnormal type (Crooke and Russell). It has been suggested that the loss of basophils may be related to the low blood pressure and possibly the hypoglycemia. Hyperplasia of the islets of Langerhans is commonly present, which may be a compensatory reaction to the hypoglycemia.

**ACUTE ADRENAL INSUFFICIENCY.**—Destruction of both adrenal glands may give rise to a fatal insufficiency which is acute instead of chronic in type. The clinical picture may be of an acute abdominal type, with severe epigastric pain, vomiting and shock; of a cerebral type with convulsions and coma; or of an asthenic type which ends fatally in a few days. In most cases the lesion is a hemorrhage or thrombosis which quickly destroys both the glands. In others the lesion may be chronic, *e.g.*, tuberculosis. No explanation can be given of the acute picture in such cases. It is probable that if the sodium concentration of the blood were to be measured it would be found to be markedly decreased.

## TUMORS OF THE ADRENAL GLAND

Primary tumors of the adrenal are rare in comparison with the relatively common hypernephroma of the kidney. Although the cortex is of mesoblastic origin, its cells are epithelial in type, so that the cortical tumors are adenoma or carcinoma. The medulla is composed of nerve cells and belongs to the chromaffin system, so that a medullary tumor may be a neuroblastoma, ganglioneuroma, or chromaffinoma.

**Cortical Tumors.**—**ADENOMA.**—Small hyperplastic nodules about the size of a pea composed of normal adrenal cortex are quite common. They do not deserve the name of adenoma. Larger masses of typical or atypical structure form more definite tumors. They are quite rare. The tumor cells are occasionally filled with yellow pigment similar to that seen in chromaffin cells, thus producing a sharp contrast between the neoplasm and the surrounding cortical cells.

**CARCINOMA.**—This rare tumor resembles the hypernephroma of the kidney in its gross appearance. It is yellow in color, often hemorrhagic, and may attain a large size (Fig. 406). Not infrequently it is bilateral. The *microscopic* picture varies in its degree of differentiation. Some cases are distinguished with difficulty from an adenoma, the acini and columns of the cortex being fairly well reproduced; although appearing rather benign, they may be quite malignant clinically. Others may be called

malignant adenoma; a suggestion of acinar grouping still remains, and the cells are large and contain lipid, but the arrangement is quite atypical and the picture evidently carcinomatous. Giant cells may form a marked feature. In a third group the structure is anaplastic, consisting of solid cords of small dark cells. Sometimes sarcomatous characters are evident in adrenal carcinoma, the cells being fusiform and arranged diffusely. Such a picture recalls the fact that the cortex is mesoblastic in origin. Some workers (Broster and Vines, Goormaghtigh) state that the masculinizing tumors present cells containing fuchsinophil granules similar to fuchsinophil cells in the so-called androgenic juxtamedullary zone of the cortex which is large at birth but small in adults.



FIG. 406.—Carcinoma of the adrenal. The tumor is entirely confined to the adrenal, and has not invaded the kidney.



FIG. 407.—Crooke's hyaline change in basophil cells.  $\times 100$ . (Kindness Dr. W. L. Donohue.)

The tumor may *spread* widely. The adrenal disappears and the kidney may be involved, so that difficulty may arise in distinguishing the tumor from a hypernephroma. This can be done by remembering that in the latter condition the adrenal is usually intact. The adrenal and renal veins are invaded, and the tumor may grow along the renal vein into the vena cava. The opposite adrenal is often affected, and metastases are common in the retroperitoneal, mesenteric and mediastinal lymph nodes, and in the liver, lungs, brain, and other organs. The bones are seldom involved; in this respect the tumor differs markedly from hypernephroma.

The *clinical picture* is of interest, as it serves to illustrate some features of adrenal physiology. In children the tumor is five times more common in girls than boys (Glynn), but in adults it is equally common in both sexes. The symptoms may be grouped in one or other of two syndromes.

(1) *The adrenogenital syndrome* is marked by hirsutism, virilism, and great muscularity, so that a boy may present the picture graphically termed the infant Hercules with premature development of the sex organs although often associated with impotence. In girls there is a development of both primary and secondary male characters; the clitoris becomes enlarged, and hair develops on the face and body (hirsutism). It is evident that here we are dealing with overactivity of the third group of corticoids, *i. e.* the androgenic and anabolic, or the nitrogen (N) hormones, which are concerned not only with sex development but also with body building. In women the sex organs atrophy, amenorrhea and obesity develop, the voice is deep, and hirsutism is marked both on the face and body. Adult males show no sexual change, except in rare cases where the tumor produces a feminizing effect.

(2) *Cushing's syndrome* is a strange clinical complex first described by Harvey Cushing in 1932 in association with small basophil tumors of the anterior pituitary. The syndrome is characterized by the following features: (1) painful adiposity which is confined to the face, neck and trunk but spares the limbs (buffalo type of obesity); (2) hirsutism in females and preadolescent males; (3) a dusky plethoric appearance; (4) peculiar striations of the skin of the abdominal wall giving an appearance of pregnancy; (5) sexual dystrophy (amenorrhea in females, impotence in males); (6) muscular weakness and atrophy; (7) kyphosis of the upper thoracic spine and generalized osteoporosis; (8) vascular hypertension; and (9) a tendency to diabetes.

Cushing believed that the syndrome was due to the basophil adenoma. Later it became evident that the important lesion was not a pituitary tumor but a tumor or hyperplasia of the adrenal cortex. But again the spotlight has shifted to the pituitary with the demonstration by Crooke that a constant finding is a peculiar hyaline change and loss of granules in the basophil cells (Fig. 407). Cushing's syndrome may be regarded as a manifestation of hyperadrenocorticism especially with respect to the glucocorticoids. This hypercorticism may be due to adrenal tumor or hyperplasia or to pituitary overproduction of ACTH, a hormone which is believed to be secreted by the basophil cells. The adiposity, the round full-moon face, and the hirsutism are all seen when ACTH or cortisone are given therapeutically for too long a period. Indeed it is this fact which had transformed Cushing's syndrome from a rare clinical curiosity to a condition of significance to every doctor using these hormones.

It must be noted that although the clinical picture caused by adrenal carcinoma may be dramatic, it is the exception rather than the rule for symptoms to develop. I have seen a tumor the size of a football which was a complete surprise at autopsy because of the total absence of endocrine symptoms.

The picture is antianabolic as evidenced by atrophy of such tissues as muscle, bone and skin, in marked contrast to the anabolic picture presented

by the infant Hercules of the adrenogenital syndrome. The glucocorticoids divert body tissue into the metabolic pool for the ultimate formation of carbohydrate and fat at the expense of muscle and bone matrix. With this in mind many of the features of the complex clinical picture become intelligible and acquire a meaning, *e. g.*, the adiposity, muscular weakness, skin striations, kyphosis and hyperglycemia. Hormonal imbalance and interference with the other corticoids may account for other features such as the sexual dystrophy.

Removal of the adrenal tumor is followed by an amazing clinical transformation, the hirsutism, adiposity, sex disturbance, etc., quickly disappearing and the patient returning to a normal condition.

Adrenal cortical tumor is one of the few conditions other than pregnancy in which an easily detectable abnormality can be found in the hormonal activity of the urine. A good index of androgenic activity of the urine is afforded by a color reaction, which is given by 17-ketosteroid compounds (steroids with a ketone group on the 17th carbon atom), among which are androsterone and dehydroandrosterone which form the main androgenic constituents of the urine. The test is referred to as the 17-ketosteroid test. The normal figure is from 10 to 20 mg. per twenty-four hours in the male and 5 to 15 mg. in the female. In cases of adrenal cortical tumor the figure is usually over 200 mg. in twenty-four hours. It may be noted by way of contrast that in Addison's disease the 17-ketosteroid excretion falls practically to zero. These facts suggest that the adrenal cortex may be the chief source of androgenic material in the urine.

**Medullary Tumors.**—The primitive sympathetic neuroblasts which form the anlage of the adrenal medulla develop either into nerve ganglion cells or into chromaffin cells (pheochromocytes). Three types of tumor may thus arise from the medulla: (1) the *neuroblastoma*, from the primitive neuroblasts; (2) the *ganglioneuroma*, from the mature ganglion cells; (3) the *chromaffinoma* or pheochromocytoma (*phaeos*, dark), from the chromaffin cells. The first is much the commonest (although itself rare), and being primitive in type is highly malignant. The other two arise from adult cells and are innocent.

**NEUROBLASTOMA.**—The tumor is almost confined to children, usually under four years of age. I have seen a case in a stillborn infant. Very rarely it may occur in adults, and I have observed a case in a boy nine years of age. It is soft and may grow to a great size. Often it is bilateral. Occasionally it does not arise from the adrenal, but from sympathetic nerve tissue in the abdomen or thorax. The microscopic picture resembles that of a sarcoma, and formerly this tumor used to be called "adrenal sarcoma of children." Most of the so-called retroperitoneal round-cell sarcomas of infants are of this character, arising from the abdominal sympathetic ganglia. The tumor consists of undifferentiated small round cells (neuroblasts), a few imperfect ganglion cells, and fibrils. The fibrils form the distinctive feature, for they are nerve fibrils and are arranged either in longitudinal bundles or in little rounded masses around which the cells are grouped in a "rosette" form (Fig. 408). These rosettes are highly characteristic of the tumor, but sometimes they are found with difficulty. They are absent in undifferentiated forms.

*Spread* of the tumor often gives rise to the formation of remarkable metastases in the skull, particularly in the orbit, so that the first sign of the disease may be the appearance of a hemorrhagic area in the neighborhood of the eye, followed later by protrusion of the eyeball (proptosis). When proptosis develops in a young child it is well to examine the abdomen. Other bones besides the skull may also be involved. This picture is referred to as the Hutchinson type. It seems likely that spread to the skull takes place by the vertebral system of veins. In other cases there is a great and uniform enlargement of the liver due to diffuse infiltration with tumor cells. The mesenteric nodes are involved. This is spoken of as the Pepper type. It is natural that tumor cells should spread more readily to the liver from the right than from the left adrenal, possibly by the lymphatics but there is little justification for the common statement that the Hutchinson type indicates a left adrenal tumor, the Pepper type a tumor in the right adrenal.

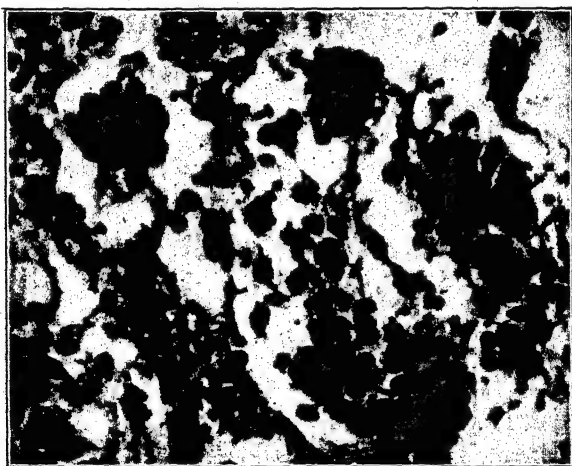


FIG. 408.—Neuroblastoma showing rosettes.  $\times 400$ .

The skeletal metastases are associated with multiple tumors in the lungs. Cases of this type are likely to be met with over the age of six months. In the Pepper type with massive liver involvement the lungs are usually spared. These cases are usually infants under six months of age. In the older group spread takes place by the post-natal circulation, but in the young infant spread may have occurred before birth. In intrauterine life most of the blood in the umbilical vein passes through the liver, whilst the lungs are by-passed by way of the foramen ovale and ductus arteriosus.

Although neuroblastoma is so malignant a tumor, not all cases are progressively fatal. Incredible though it may sound recovery may take place either spontaneously or following radiation (Farber). In one case at the Toronto Sick Children's Hospital part of the tumor was removed but the remainder had to be left in the abdomen, yet the child made an uninterrupted recovery, and was alive and well four years later. (I saw her.)



**GANGLIONEUROMA.**—This rare form of innocent tumor occurs both in children and adults, and is found in the brain and abdominal sympathetic as well as in the adrenal medulla. It is composed of adult ganglion nerve cells, spherical or pyramidal, and nerve fibers which may be medullated or non-medullated.

**PHEOCHROMOCYTOMA** (*phaeos*, dark).—This rare tumor is also known as chromaffinoma and paraganglioma. It is usually innocent, small, well encapsulated, and may be found by accident at autopsy in elderly persons. Several cases which I have studied have presented a characteristic cystic degeneration. The tumor may be brown in color. About 20 per cent of the cases are said to be bilateral, and these are usually malignant. Occasionally it may attain a great size, as in one case reported by Soffer and his associates where the tumor weighed 2000 grams. The most interesting clinical feature is the frequent occurrence of arterial hypertension, usually paroxysmal in type, for the tumor contains a large amount of adrenalin, often much more than the normal adrenal, and a pressor substance can be demon-

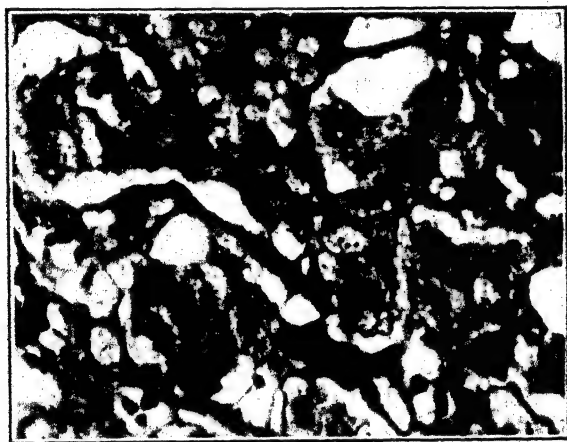


FIG. 409.—Pheochromocytoma. The large ragged cells resemble those of the adrenal medulla.  $\times 320$ .

strated in the blood. During the attacks the systolic blood pressure may rise to 250 or even 300 mm. of mercury, and an accompanying hypoglycemia may lead to shock. The attack may last for minutes or hours, and if prolonged it may prove fatal. The tumor may be demonstrated radiographically by perirenal insufflation or by depression of the renal pelvis in a pyelogram. These tumors are found in other parts of the chromaffin system, such as the carotid body, the abdominal paraganglia and the organ of Zuckerkandl at the bifurcation of the aorta. It is best to use the name chromaffinoma for the whole group, pheochromocytoma for the adrenal tumors, and paraganglioma for the extra-adrenal tumors. The tumor is composed of large epithelium-like cells (Fig. 409) which are often pigmented and may stain brown when fixed in chrome salts. In a number of cases there has been an associated neurofibromatosis.

*Secondary tumors* are quite common in bronchogenic carcinoma and are frequently bilateral; much less often they are due to cancer of the breast and other organs. They are usually in the medullary portion. Bilateral tumors may in rare instances cause Addison's disease.

## DEGENERATIONS OF THE ADRENAL GLANDS

Postmortem change in the adrenal glands is extremely common, and must not be mistaken for evidence of disease. The inner layer of the cortex softens, and is converted into a brown mush, so that only a rind of cortex is left. Various acute infections produce damage leading to necrosis of isolated cells, and a striking transformation of the solid cords of the zona fasciculata into tubular structures resembling renal tubules and containing an acute inflammatory exudate (Rich). Such lesions may serve to explain the circulatory collapse of acute infections. Massive hemorrhage is rather frequent in the new-born, and when bilateral it may be a cause of death. The hemorrhage follows the necrosis of the inner layer of the cortex which always occurs at birth, possibly as the result of the sudden withdrawal of the female sex hormone. Fatal massive hemorrhage is not confined to this age. It is apt to occur in meningococcal septicemia, and the combination with this infection and massive bilateral adrenal hemorrhage is known as the *Waterhouse-Friderichsen* syndrome. This is marked by acute and fatal peripheral circulatory collapse. It is a mistake, however, to think that adrenal hemorrhage is a necessary factor in the production of this calamity. Fulminating meningococcal infection with the formation of widespread hyaline capillary thrombi will give the same result without adrenal hemorrhage. (Ferguson and Chapman). The cortical lipid disappears quickly in acute infections, more slowly in chronic infections and anemia, and is increased in arteriosclerosis, chronic nephritis, and nephrosclerosis. Amyloid degeneration affects the adrenal at the same time as the liver, spleen, and kidney, with enlargement and hardening of the gland.

Myeloid metaplasia with formation of bone marrow is occasionally seen. The stroma of the adrenal may contain fat cells and cells filled with large lipid granules. Small foci of round cells are often noted, particularly when death has been due to carcinoma and myocardial infarction, conditions in which there may be stimulation by toxic products from necrotic tissue. Selye and Stone have reported myeloid metaplasia of the adrenal from the administration of crude anterior pituitary extract.

## ADDITIONAL READING

- Addison's Disease.** CROOKE AND RUSSELL: *J. Path. and Bact.*, 1935, 40, 255. GUTTMAN: *Arch. Path.*, 1930, 10, 742. HINERMAN: *Arch. Path.*, 1951, 51, 539. WELLS: *Arch. Path.*, 1930, 10, 499. WELLS, *et al.*: *J. A. M. A.*, 1937, 109, 490.
- Adrenal Hemorrhage of Infancy.** RABINOWITZ: *Am. J. Med. Sci.*, 1923, 166, 513.
- Adrenal in Anencephalic Monster.** ANGEVINE: *Arch. Path.*, 1938, 26, 507.
- Adrenal Tumors.** GESCHICKTER: *Am. J. Cancer*, 1935, 23, 104.
- Adrenal Virilism.** BROSTER AND VINES: *The Adrenal Cortex*, London, 1933. BROSTER, *et al.*: *The Adrenal Cortex and Intersexuality*, London, 1938.
- Changes in Acute Infections.** RICH: *Bull. Johns Hopkins Hosp.*, 1944, 74, 1.
- Cholesterol Content.** ROGERS AND WILLIAMS: *Arch. Path.*, 1948, 46, 451.
- Cortical Tumors.** CAHILL, *et al.*: *Surg., Gynec. and Obst.*, 1936, 62, 287. GLYNN: *Quart. J. Med.*, 1911, 5, 157. GOORMAGHTIGH: *Am. J. Cancer*, 1940, 38, 32.
- Cortisone.** HENCH: *Ann. Int. Med.*, 1952, 36, 1 (Nobel Lecture).
- General References.** GROLLMAN: *The Adrenals*, Baltimore, Md., 1936. HARTMAN AND BROWNELL: *The Adrenal Gland*, Philadelphia, 1949. SOFFER: *Diseases of the Adrenals*, Philadelphia, 1946.

- Myeloid Metaplasia.** SELYE AND STONE: *Am. J. Path.*, 1950, 26, 211.
- Neuroblastoma.** BLACKLOCK: *J. Path. and Bact.*, 1934, 39, 27. FARBER: *Am. J. Dis. Child.*, 1940, 60, 749. FREW: *Quart. J. Med.*, 1911, 4, 123. HUTCHINSON: *Quart. J. Med.*, 1907, 1, 33.
- Pheochromocytoma.** BLACKLOCK, *et. al.*: *Brit. J. Surg.*, 1947, 35, 179. BRUNSCHWIG AND HUMPHREYS: *J. A. M. A.*, 1940, 115, 355. GREEN: *J. A. M. A.*, 1946, 131, 1260. HYMAN AND MENCHER: *J. Urol.*, 1943, 49, 755. SOFFER, *et. al.*: *Surg. Clin. N. Amer.*, 1946, 26, 368.
- Stress.** ARNOLD: *Hawaii Med. J.*, 1952, 11, 358. PICKERING: *Lancet*, 1950, 1, 81. SELYE: *The Physiology and Pathology of Exposure to Stress*, Montreal, 1950.
- Tumors of the Adrenal.** CAHILL AND MELICOW: *J. Urol.*, 1950, 64, 1.
- Waterhouse-Friderichsen Syndrome.** FERGUSON AND CHAPMAN: *Am. J. Path.*, 1948, 24, 763. MARTLAND: *Arch. Path.*, 1944, 37, 147.

## THE THYROID GLAND

**GENERAL CONSIDERATIONS.**—The thyroid gland is one of the most labile organs in the body. It is continually being played upon by various influences (endocrine, etc.), and responding to the varying demands of thyroxin. On this account the structure is not fixed, any more than the structure of the breast or endometrium is fixed. Physiological variations as evidenced by a certain amount of hyperplasia and involution are common in autopsy specimens, although in some cases no doubt they are terminal. Such compensatory hyperplasia is not necessarily associated with any symptom of hyperthyroidism. The pathological thyroid gland differs from the normal in degree rather than in kind of change, and it is often extremely hard to draw a line between the two. It may well be that under normal conditions the acini of the thyroid are in various phases of function, which may be called the resting, secretory and resorptive phases (Halpert). In the resting phase the acini are large, lined by flattened cells, and filled with deeply stained homogeneous colloid. This is the picture in colloid goiter and in the gland of hyperthyroidism treated with a solution of iodine. In the secretory phase the acini are lined by cuboidal epithelium and the colloid is stained moderately darkly. This is the picture seen in the normal thyroid. In the resorptive phase the acini are lined by columnar epithelium, and contain lightly stained, vacuolated and scalloped colloid. This is the picture seen in hyperthyroidism and in patients treated with thiouracil. The normal thyroid gland in non-goitrous districts weighs from 25 to 35 grams, but it weighs more in women than in men, more in the summer than the winter, more during pregnancy and lactation, and more in goitrous districts even though it may appear to be quite normal.

The chief function of the thyroid gland is to maintain a higher rate of metabolism, as evidenced by heat production, than would otherwise be possible, and to regulate this rate according to the needs of the body. This is done by means of its iodine-containing hormone, thyroxin. The physiological effect of feeding thyroid gland is to raise the rate of metabolism. Removal of the thyroid gland is followed not only by a loss of heat production, but in the growing animal by poor physical, mental and sexual development. The thyroid gland has a remarkable affinity for iodine, and is the only organ in the body which has the power of storing that element. The iodine content of a dog's thyroid can be increased several hundred per cent in the space of five minutes by the intravenous injection of 50 mg. of potassium iodide. The rapidly stored iodine is at first inactive, but gradually becomes converted into an active form. The active principle of the gland contains 65 per cent of iodine. Apparently the iodine is converted by the epithelium of the acini into thyroxin. Some of this passes into the circulation in response to the demand of the tissues. The rest is stored in the form of colloid within the acini, where it con-

stitutes an emergency ration which can be used when the need arises. The normal iodine content of the gland is about 0.2 per cent. If it falls below 0.1 per cent morphological changes at once become apparent in the acinar epithelium, and the gland becomes enlarged in consequence. This fall may be due to an increased demand on the part of the tissues for thyroxin, or to an inadequate supply of iodine to the gland. The morphological changes are hypertrophy and hyperplasia of the acinar epithelium together with an increased vascularity. As a result of this cellular activity the emergency ration in the colloid is made use of and depleted, and the demand of the tissues for thyroxin is met. If this demand is moderate the hypertrophy may be regarded as physiological; when it is excessive or long-continued the response of the thyroid becomes pathological. When the iodine supply is insufficient the epithelial activity is an indication that the gland is engaged in the attempt to make bricks without sufficient straw, and if the strain is not too great the attempt may be successful. The administration of iodine, even in minute doses, soon relieves the strain, and the epithelial activity subsides, while the iodine-containing colloid collects once again within the acini. The process is known as involution.

In dogs and in other experimental animals the process of hyperplasia is diffuse, so that there is a uniform enlargement of the entire gland. In man, on the other hand, it tends to be patchy and localized, with the result that nodules tend to be formed. These are known as adenomas, although in the great majority of cases they are not true tumors, so that the name is misleading. Some of these nodules or adenomas respond to iodine treatment like the rest of the gland, but others may not.

An intimate relationship exists between the thyroid and the anterior pituitary, a mechanism which has been called the pituitary-thyroid axis. The thyrotropic hormone of the pituitary is the most powerful known stimulant of thyroid activity. In the experimental animal it causes extreme enlargement of the gland, great epithelial hyperplasia, and corresponding elevation of the basal metabolic rate. The pituitary itself is under the influence of nervous stimuli from the hypothalamus, the controlling center of emotional activity. It is evident that emotional disturbance may be expected to play a part in thyroid hyperactivity. The thyrotropic hormone is also responsible for the exophthalmos which accompanies Graves' disease. Here the action appears to be through the cervical sympathetic on the orbital tissues. There is a two-way traffic on the pituitary-thyroid axis, the thyroid hormone inhibiting the production of the thyrotropic hormone, so that in health a balance is maintained.

Certain sulphur-containing substances cause a curious dissociation of the usually associated thyroid hyperplasia and increased basal metabolic rate, stimulating the former and depressing the latter. Chief amongst these are the sulphonamide drugs and sulphur-containing thiourea and its non-toxic derivative thiouracil. They appear to prevent the synthesis of thyroxin at a normal rate, the accompanying thyroid hyperplasia being an attempt to compensate for this defect. Iodine, on the other hand, when given to control the thyrotoxicosis of Graves' disease appears to push the finished product into the warehouse (thyroid follicles), and thus prevent free distribution of thyroxin to the body. The two groups of agents thus act at different points of the hormone assembly line (Means).

**Goiter.**—This is an indefinite term applied to enlargement of the thyroid. From what has been said it is evident that theoretically this enlargement might be evidence: (1) of a primary hyperplasia; (2) of a compensatory hyperplasia to meet increased demands of the tissues for hormone; and (3) of increased storage of colloid.

There is no satisfactory *classification* of goiter. It is usual to recognize three main types: diffuse colloid goiter, exophthalmic goiter (Graves' disease), and nodular or adenomatous goiter. It will be noticed that the first type is named from a microscopic feature, the second from a leading symptom (which may be absent), and the third from the gross appearance. This is hardly a satisfying or scientific basis, but it is the best we have. The clinicians speak of diffuse non-toxic and toxic goiter and adenomatous non-toxic and toxic goiter. This is quite justifiable, but the pathologist is unable to relate these terms to morphological changes in the thyroid. The terms toxic and thyrotoxicosis indicate a clinical picture similar to that produced by overdosage with thyroid extract. Whether or not the three main forms of goiter are separate entities is a matter of dispute. While it is true that extreme examples differ enormously from one another, yet intermediate types will be found to bridge the gaps, clinical as well as pathological. In spite of this it is possible that different etiological agents are operative in the different forms.

The *geographic pathology* of goiter varies greatly (Hellwig). This serves to explain the conflicting accounts which are found in the writings of observers in different parts of the world. The goiter of North America, for instance, is very different from that of the Himalayas and the Alpine districts of Switzerland. In the former the common variety is the diffuse and nodular colloid goiter with large acini distended with colloid (macro-follicular type), whilst in the latter parenchymatous goiter is the usual form characterized by small follicles poor or lacking in colloid (micro-follicular type). Thyrotoxic symptoms are commoner in North America than in any other country. Thus in Berne, Switzerland, 3 per cent of goiters are associated with thyrotoxicosis, whereas in Portland, Oregon, 67 per cent fall in the toxic group. In mountainous countries the microfollicular non-toxic type is prevalent; in level countries the macrofollicular, often associated with toxic symptoms, is common.

### DIFFUSE COLLOID GOITER

This type of goiter includes those varieties known as simple goiter, endemic goiter and adolescent goiter, although these various terms are by no means synonymous. It is the most physiological form of thyroid disease, for it commences as a compensatory or work hypertrophy, but physiological limits in the thyroid are easily transgressed, and when the gland has met the demand of the tissues it may be unable to return to its former size.

The main *causal factor* in endemic goiter is an insufficient supply of iodine to the thyroid, which in consequence develops a work hyperplasia followed later by involution. The soil of high countries is denuded of iodine, so that the drinking water is poor in that element. In the endemic region of North America, particularly the region of the Great Lakes and the valley of the St. Lawrence, the soil is iodine-poor, having been deposited from the melting of the ice of the last glacial epoch. Animals as well as men living in endemic regions suffer from simple goiter. This type of goiter is a deficiency disease due to lack of iodine.

Simple colloid goiter is much commoner in women than in men. It commonly appears in girls at the time of puberty or soon after. It tends to disappear after a few years, so that the usual age period is from fifteen to twenty-five years. In endemic regions the condition tends to appear earlier and last longer. It may be due to a relative rather than an absolute lack of iodine. There may be enough iodine in the food and water for ordinary purposes, but not for the increased demand for thyroxin at adolescence and puberty. Similar enlargement may occur during pregnancy and lactation and for a similar reason. Such goiter responds remarkably to the administration of iodine when in the hyperplastic stage. "The normal physiological rhythm of colloid storage during rest and colloid release during

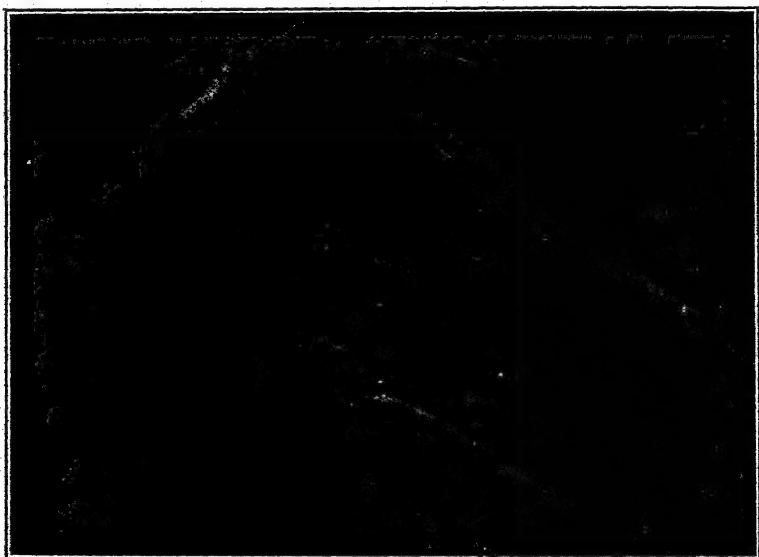


FIG. 410.—Colloid goiter. The acini vary much in size, some being widely dilated. The colloid is abundant and stains deeply. The epithelium is flattened.  $\times 75$ .

activity is changed into a different gear by the demands of puberty, pregnancy and parturition. Undue stress and strain will eventually throw this finely equilibrated balance out of rhythm." (Levitt).

**LESIONS.**—It is very seldom that one has the opportunity to study the goiter of adolescence during the hyperplastic stage, for it should never be removed surgically. When the gland is removed in the involutionary or colloid stage, as may have to be done on account of its increasing size, it is found to be uniformly and diffusely enlarged and of soft consistence. The cut surface is amber in color, and presents a finely honey-combed translucent appearance, owing to the distended acini being filled with colloid.

The *microscopic appearance* may resemble that of normal thyroid tissue, but there is greater irregularity. Many acini are greatly enlarged. Some are of normal size and some are smaller than normal. All are filled with

densely stained colloid (Fig. 410). The epithelium is low, and in the larger acini it may be flattened. A few small islands of hyperplasia may still be present, and evidence of former hyperplasia is apparent in the form of withered spurs which still project here and there from the acinar walls.

### NODULAR OR ADENOMATOUS GOITER

As the years pass a goiter tends to become nodular. Some of these nodules may be new formations of tissue, so that they are called adenomas. Some may be associated with symptoms of thyrotoxicosis, so that they are referred to as toxic adenomas. There is no difference in structure between toxic and non-toxic adenomas. They merely cause pressure symptoms. The number increases with age.

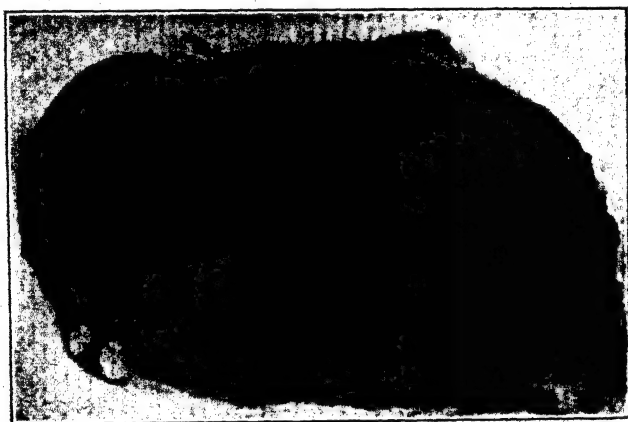


FIG. 411.—Nodular goiter. The large nodules are of the colloid type, while the small nodules at the bottom left-hand corner are of the fetal type.

Adenomatous goiter is the common type of goiter demanding surgical treatment in North America. The nodule may be single, but more often it is multiple (Fig. 411). The larger nodules are well encapsulated. Degenerative changes such as softening, cyst formation and hemorrhage are common. When a thyroid nodule suddenly enlarges it is probably due to hemorrhage into a cyst. Calcification is frequent. The *microscopic appearance* is the same as that of the surrounding gland. It may or may not show hyperplastic changes. These may be more marked than those of the surrounding gland. In young persons the lesion is often the so-called fetal adenoma, because of the resemblance to the fetal thyroid. The cut surface in such a case is dense, opaque and pale, and the adenoma is composed of small acini with little or no colloid. This is the picture of the microfollicular parenchymatous goiter so common in the endemic regions of Europe, although that lesion is diffuse and not localized. Mucoid degeneration may cause the acini to be widely separated (Fig. 412). Sometimes the tumor consists of solid masses of cells without any attempt at acinar formation (Fig. 413). Such lesions suggest a true tumor.



FIG. 412.—Adenoma of the thyroid. The acini are very small and are widely separated by a structureless material. The vessels are markedly dilated. There is apparent budding of the acinar epithelium, with formation of new acini.  $\times 250$ .

The *relation of nodular goiter to carcinoma* is far from settled. Some authorities state that some 10 per cent of all nodular goiters are malignant, whilst others differ sharply from this view. The chief reason for this divergence of opinion is that it is often difficult and sometimes impossible to draw a hard-and-fast line between the benign and malignant adenoma. This can be seen from the fact that Graham, a leading authority on the subject, analyzing 186 cases previously diagnosed as malignant adenomas, felt compelled to reclassify 106 cases as benign because they had survived for six or more years without recurrence. Even this criterion is open to question. The matter is of great practical importance, because the course taken by the surgeon in the treatment of a thyroid adenoma will be determined by the view which he favors.

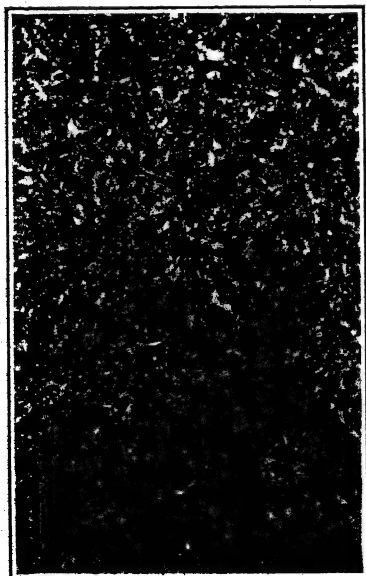


FIG. 413.—Adenoma of thyroid; solid collections of acini.  $\times 275$ .

#### EXOPHTHALMIC GOITER— GRAVES' DISEASE

Graves' disease is an enigma and constitutes one of the most perplexing problems in the whole of medicine, for it provides an example of an organ



starting and continuing to hyperfunction without any regard to the needs of the body. It bears no apparent relation to iodine deficiency. There is often a very definite history of nervous or psychic shock, not infrequently sexual in character. In some cases the onset of the disease has followed such a shock within a few days. The tendency at present is to look beyond the thyroid in seeking the essential cause of Graves' disease. The pituitary is a possibility, since the thyrotropic hormone of that gland is the most powerful stimulator of thyroid hyperplasia. As there is excitement of the sympathetic system the adrenals may play a part. Most persons who develop Graves' disease belong to a certain type, the so-called Graves' constitution. They are of slender build, temperamental, easily overstimulated, with rapid pulse and slight tremors, and especially sensitive to the administration of thyroid extract. It would appear that in such persons something serves to upset the normal balance which should exist between the ductless glands (pituitary, adrenals, thyroid), one result of which is overstimulation of the thyroid, and that this balance may never be permanently regained.

**SYMPTOMS.**—The disease is much commoner in women than in men in the proportion of 5 to 1. It usually begins in early adult life and the onset is often sudden and acute. When it develops in later years the onset is more gradual. The symptoms of Graves' disease are due to excitation of the sympathetic system. The four cardinal signs are enlargement of the thyroid, exophthalmos, tachycardia, and tremors. The skin is moist and liable to vasomotor disorders such as flushing; the patient is excitable; palpitation, diarrhea, and vomiting may occur; there is loss of weight and an enormously increased body metabolism as indicated by calorimetric observations. The course of the disease varies. It may be acute and fulminating, the patient dying with all the classical symptoms of exophthalmic goiter; sometimes he dies in a so-called thyroid storm after thyroidectomy. In other cases the course is less violent, and is marked by a series of remissions and exacerbations. Gradually the fire burns itself out, the thyroid breaks down under the constant stimulation, and a condition of partial thyroid insufficiency (myxedema) may develop. There is profound disturbance in iodine metabolism, as indicated by raised blood iodine, increased excretion of iodine, and a negative iodine balance. This increased mobilization of iodine in hyperthyroidism resembles the disturbed calcium metabolism of hyperparathyroidism.

**LESIONS.**—The thyroid gland is moderately or considerably enlarged, but the largest goiters do not occur in Graves' disease but in the adenomatous and colloid forms. It must be remembered that no enlargement may be detected clinically, as the hypertrophied lobes may be behind the trachea. The gland, over which greatly dilated veins may course, is firm, pink in color owing to the increased vascularity, and of a dense meaty appearance which is in marked contrast to the translucency of the normal thyroid. If the patient has been given iodine (Lugol's solution) before the thyroid gland was removed, the characteristically dense appearance is lost owing to the temporary change from a hyperplastic to a colloid condition. The enlargement is diffuse, but the cut surface shows a fine lobulation which, together with the meaty appearance, suggests a resemblance to the cut surface of the pancreas.

The *microscopic picture* shows three characteristic changes: epithelial hypertrophy and hyperplasia, disappearance of colloid, and lymphoid

hyperplasia. The epithelium is tall and columnar, and mitotic figures may be numerous. The acini are greatly enlarged and very irregular, but this enlargement is not readily obvious unless a wax reconstruction is made, for they are filled with the papillary processes which form in order to accommodate the new formation of cells (Fig. 414). Sometimes there is no enlargement of acini with infolding of their walls, but a formation of great numbers of small rounded acini lined by columnar epithelium. In both forms the colloid is thin and scanty or has completely disappeared. The change in the colloid is most marked where it comes in contact with the lining epithelium, as if it is being absorbed by the acutely active cells.

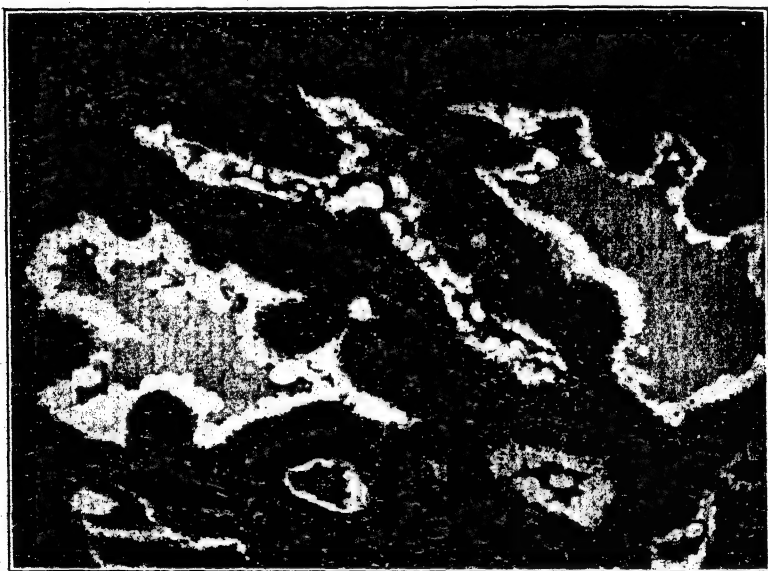


FIG. 414.—Thyroid of Graves' disease undergoing involution under iodine treatment. The papillary processes are being withdrawn from the enlarged acini, and the colloid is reappearing. Above and below there is still dense hyperplastic tissue.  $\times 150$ .

Scattered throughout the stroma are lymphoid follicles with definite germinal centers (Fig. 415), in addition to which there may be a more diffuse infiltration with lymphocytes. The lymph follicles become larger and more distinct after prolonged treatment with Lugol's solution. It is probable that they are a result of the hyperplasia and hypersecretion of the thyroid. Wegelin points out that the lymphoid tissue in the thyroid appears to be developed as a purely local response to irritation and not as part of a thymico-lymphatic constitution. There is a marked increase in the vascularity in keeping with the general increase in glandular activity.

When the patient has had a short preoperative course of Lugol's solution the picture is markedly changed, corresponding with the great abatement in the symptoms of thyrotoxicosis. The epithelial hypertrophy and hyper-

plasia subside, colloid reappears, and the lymphoid tissue is less abundant. But when the administration of iodine is prolonged for weeks or months a different picture develops, which bears a spurious resemblance to the resting colloid gland. Epithelial hypertrophy is still absent and the atrophic looking follicles are lined by a low type of cell, but the colloid is thin and watery, lymphoid hyperplasia is very marked, the germinal centers of the follicles are remarkably large and pale, a condition which Warthin calls lymphoid exhaustion, and there is proliferation of the stroma. The symptoms meanwhile may have returned in full force.



FIG. 415.—Hyperplastic thyroid showing an extreme degree of lymphoid hyperplasia. The patient had been treated with Lugol's solution.  $\times 40$ .

Thiouracil, a derivative of thiourea, produces a curiously contrasted effect. The clinical symptoms of hyperthyroidism are relieved and the basal metabolic rate lowered, but the resorptive phase of thyroid physiology appears to be intensified, for the colloid is diminished in quantity and density and may finally disappear, whilst the epithelium is tall and columnar. The picture resembles the histology of toxic goiter before the days of preoperative preparation with iodine. Thiouracil thus appears to inhibit the production of new colloid, but does not interfere with the use of the available colloid (Halpert).

*Lesions in other organs* deserve at least passing mention. The hyperplasia of the *thymus* and *lymphoid tissue* has already been mentioned. A persistent and enlarged thymus is found at autopsy in the majority of cases of typical exophthalmic goiter. The lymph nodes, tonsils, Peyer's patches, and lymphoid follicles in the spleen may all show hypertrophy similar to that of status lymphaticus. In some of my fatal cases there has been tremendous lymphoid hyperplasia of the appendix,

the lymphocytes obliterating the mucosa and lumen and infiltrating the muscular wall. The *blood* shows a relative lymphocytosis. The heart is often enlarged, and may show myocardial degeneration and fibrosis, but there are no specific lesions. The *muscles* may show fatty degeneration. This can hardly account for the muscular weakness, which may manifest itself in the difficulty the patient has in lifting his foot to a height (quadriceps sign). Sometimes the muscular weakness is the most prominent clinical feature, a condition known as chronic thyrotoxic myopathy. The basis of this disorder may be a deficiency of steroid hormone, as indicated by low urinary excretion of 17-ketosteroids, testicular atrophy and degeneration of the adrenal cortex (Thorn and Eder). In the *orbit* there is an increase of fat and water content, and the orbital muscles are invaded by fat and lymphocytes. It may be that the orbital changes are merely a local exaggeration of a generalized myopathy. The *adrenals* may be atrophic, but there are no specific lesions. The *liver* often shows passive congestion, and degenerative lesions are common. Fatty change is extremely frequent. There may be acute necrosis, both focal and central. Cirrhosis has been reported in from one-third to one-half of the cases. It is most marked in the subcapsular zone. Moschocowitz believes that it is similar to cardiac cirrhosis, although originating in the interlobular septa rather than around the central vein, and considers the pathogenic factor to be increased velocity of blood flow which upsets the pressure relationship between the hepatic artery and the portal vein, resulting in stasis, capillary sclerosis, and eventually fibrosis. Liver function tests often show a marked degree of impairment. It has been suggested by Boyce that in thyrotoxicosis the overstimulated metabolism results in combustion of the protective glycogen of the liver beyond the degree of safety. When that point is reached there develops sudden and extreme hyperpyrexia, an almost uncountable pulse, vomiting, diarrhea, and restlessness which may pass into delirium, coma and death. This picture is known as thyroid crisis or thyroid storm. The *bones* often show marked rarefaction and decalcification due to a lacunar absorption brought about by osteoclasts and associated with a great excretion of calcium.

**THE RELATION OF SYMPTOMS TO THE LESIONS OF GOITER.**—*Diffuse colloid goiter* usually produces no symptoms, except possibly those of pressure. On the other hand there may be mild degrees of thyrotoxicosis or of hypothyroidism. Microscopic examination of the thyroid fails to give a satisfactory explanation of these differences. The parenchymatous, microfollicular, colloid-poor goiter so prevalent in the mountainous regions of Europe is hardly ever associated with toxic symptoms.

In *Graves' disease* the cardiovascular phenomena and the increased basal metabolic rate are manifestations of hyperthyroidism, which itself is presumably caused by epithelial hyperplasia. But there are difficulties. A patient may have well marked symptoms of hyperthyroidism without epithelial hyperplasia, especially when iodine treatment has been too prolonged. Goiter in adolescents in regions of severe goiter may show all the microscopic changes characteristic in Graves' disease, yet thyroid function may be normal. The administration of thyroxin does not produce the exophthalmos and other neurological phenomena of Graves' disease. Indeed exophthalmos may get worse after removal of the thyroid, so-called malignant exophthalmos developing after operation may destroy the eyeball. There is no agreed explanation for the exophthalmos, but in severe cases the extraocular muscles and orbital connective tissue may be greatly swollen owing to edema. Exophthalmos associated with orbital edema can be produced experimentally by injection of the thyrotropic hormone of the anterior pituitary, even though the thyroid has first been removed. This is due to a mucoid type of edema of the orbital fat, which is particularly rich in loose connective tissue and is therefore readily infiltrated. It seems probable that the stimulus responsible for the exophthalmos is the thyrotropic hormone of the pituitary acting through the cervical sympathetic

on the orbital tissues. Thyroidectomy removes the inhibitory effect of the thyroid on the pituitary, thus explaining the occasional postoperative intensification of the exophthalmos. It has been suggested that in Graves' disease the thyroid allows thyroxin to leak from the gland (thyroid diarrhea), and that the hyperplasia is an attempt to compensate for the rapid loss of hormone, and therefore merely a secondary phenomenon. This sounds well, but it may have more sound than meaning.

The chief symptom of *adenomatous goiter* is local pressure on the trachea, which may cause marked narrowing of that structure with dyspnea. Hemorrhage into an adenomatous cyst may aggravate the condition in a sudden and alarming manner. A *retrosternal goiter*, usually due to the downward extension of an adenoma, is a cause of dyspnea which may escape detection for some time. *Thyrototoxicosis* may or may not be present; the adenoma is said by the clinician to be toxic or non-toxic. The validity of the concept of toxic adenoma has long been disputed, but the matter has now been settled by the use of tracer doses of radioactive iodine. The uptake of labelled iodine is an index of the rate of secretory activity of the thyroid cells as shown by an externally applied Geiger counter or by autoradiograms with excised tissue. In toxic adenoma the tumor alone is actively secreting, whereas in Graves' disease the entire gland is active. In both the epithelium is taller than in the normal thyroid. The non-toxic adenoma may take up no labelled iodine. As shown by this test, malignant tumors secrete very slightly or not at all. It is extremely rare to find carcinoma in a thyrotoxic gland, whether adenomatous or diffusely hyperplastic. Indeed hyperplasia and malignancy are largely exclusive

## CRETINISM AND MYXEDEMA

Deficiency of the thyroid secretion gives rise to very characteristic symptoms and may be caused in a variety of ways. The basis of the condition may be congenital or acquired. The former is known as cretinism, the latter as myxedema.

**Cretinism.**—If the thyroid does not develop properly during fetal life, or if it is acted on during that period by goitrogenous influences, the child is born a cretin. Cretinism may be endemic or sporadic. The *endemic* form is common in the great regions of endemic goiter, the Alps and the Himalayas. It has been said that goiter is the first step on the road to cretinism. The mother almost always suffers from simple (endemic) goiter. The child at birth does not have a goiter, but in a few years he usually develops one unless removed to a non-goitrous district. At first the thyroid may show a compensatory hyperplasia, but later there is exhaustion atrophy although the gland is still enlarged. Endemic cretinism can be prevented by giving the pregnant woman a sufficient amount of iodine. The *sporadic* form occurs in non-endemic regions. The cause is not known, but is apparently something that interferes with the development of the thyroid, which is represented by a fibrous remnant. Indeed it may be difficult to find any trace of thyroid tissue, so that goiter does not develop.

The cretin is a dwarf physically and mentally. The mind, the skeleton, and the sexual organs do not develop. Like Peter Pan, the cretin never grows up, but he has none of Peter's vivacity for the vitalizing influence of the thyroid is lacking. He is a sad, old child. The stature is stunted, the head large, the face broad, the features coarse, the arms short and curved, the sexual organs undeveloped, and the mental powers little better than those of an imbecile. What was intended to be created in the image of God has

become what has been called the pariah of Nature, and all for want of a little iodine.

**Myxedema.**—This is the condition of thyroid deficiency in the adult, and usually appears about the age of forty years. It is commoner in women. It has no relation to goiter, and is not commoner in the regions of endemic goiter. It may be due to some extrathyroid cause, such as pituitary deficiency. Some cases of Simmonds' disease (pituitary insufficiency) may simulate myxedema, for in that condition there is atrophy of the thyroid; this has been called the pituitary type of myxedema (Means). Usually, however, there is no clinical evidence of pituitary disease in myxedema, nor any significant histological changes in the pituitary. The thyroid gland

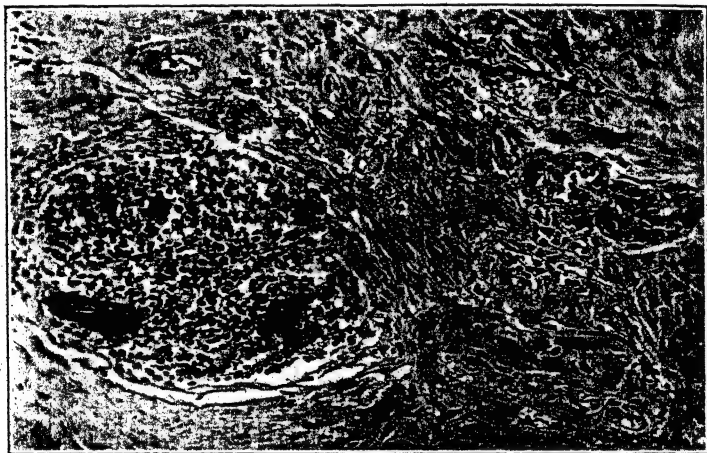


FIG. 416. The thyroid in myxedema. The glandular tissue has been replaced by fibrous tissue; remnants of acinar epithelium remain surrounded by lymphocytes.  $\times 125$ .

is atrophic, hard, and in the most severe cases is converted into a mass of fibrous tissue. As a rule areas of atrophic glandular tissue remain separated by an abundant fibrous stroma. Lymphoid collections are frequent, and are probably related to the disappearing parenchyma as in chronic nephritis. (Fig. 416.)

The *clinical picture* in an advanced case is so characteristic that the diagnosis can be made at a glance, but owing to the efficacy of treatment with thyroid extract such cases are seldom seen nowadays. The woman is heavy and intensely phlegmatic, the face broad and devoid of all expression, the skin rough, dry, and singularly sensitive to cold. Persons with hyperthyroidism have a moist skin and rarely feel the cold, those with hypothyroidism have a dry skin and continually feel cold because the metabolic fire is burning so low. The hair is dry and falls out, often beginning first in the outer third of the eyebrows. The basal metabolic rate is characteristically low. The serum cholesterol is invariably high in untreated cases and decreases on treatment. Its estimation is therefore of

great value in the diagnosis of myxedema, and it is a better indicator than the basal metabolic rate, as it is less dependent on the coöperation of the patient. It must be remembered that cases encountered in practice are not likely to show this full-blown picture, and have to be recognized when the symptoms are much less marked.

The disease owes its name to a solid pseudoedema of the skin and mucous membranes caused by infiltration with an acid mucopolysaccharide (hyaluronic acid) so that the tissue appears to be myxomatous. It is this infiltration which serves to iron out the expressive wrinkles and folds of the face, so that all the patients have a strong family resemblance to one another. The change is most marked in the face, neck, supraclavicular fossæ and the backs of the hands, which are fat and clumsy. The mucous membranes are also infiltrated, so that the tongue is thick, and there is swelling of the mucous membrane in the nose, mouth, larynx, bronchi, and alimentary canal. The heart may appear to be markedly enlarged on clinical and roentgenological examination (myxedema heart). This is in the main due to pericardial effusion, in part to myxomatous infiltration of the myocardium and dilatation of the chambers. The enlargement of the heart shadow rapidly returns to normal under thyroid therapy. The edema, which may be associated with serous effusion in the pericardial cavity, may be dependent on a change in the capillary permeability, which can be shown experimentally to be markedly increased in myxedema (Lange). With thyroid therapy the permeability rapidly returns to normal. Cardiac edema is not associated with increased capillary permeability. There is advanced atrophy of the interstitial cells of the testis, accounting for such gonadal symptoms as impotency and loss of desire (Marine).

*Cachexia strumipriva* is postoperative myxedema caused by too radical removal of a goiter (struma). The condition, which is characterized by marked wasting as well as the ordinary symptoms of myxedema, was common in the early days of goiter surgery, but is very rarely seen at the present time.

## TUMORS OF THE THYROID GLAND

**Carcinoma.**—Carcinoma commonly arises in a preëxisting adenoma. The relation of adenomatous goiter to carcinoma has already been discussed on page 710. The adenoma may be quite small, it is generally non-toxic, and the malignant change may occur in youth or even in childhood. Carcinoma is commoner in women than in men, because of the much higher incidence of nodular goiter in the female. Wegelin points out that in Berlin where the incidence of goiter is low there were 13 malignant tumors of the thyroid in 13,426 autopsies, whereas in Berne where the incidence of goiter is high, there were 159 malignant tumors in 15,250 autopsies. It bears no relation to Graves' disease. This is strange, because in that disease there is a wilder epithelial proliferation than in any other non-neoplastic lesion. The tumor is hard and rapidly growing, causing pressure on the trachea with dyspnea. There is pain and fixation to the surrounding parts. All of these features are present in Riedel's struma (see p. 721). The tumor at first shares the capsule of the adenoma, but later infiltrates



the surrounding gland and invades the regional lymph nodes. Long before this happens distant metastases may have been set up by early invasion of the blood vessels. Carcinoma may sometimes cause symptoms of hyperthyroidism.

The *microscopic picture* varies greatly and many different names have been applied, but it is sufficient to recognize adenocarcinomatous, medullary (Fig. 417), and scirrhou forms. The last is quite rare. The adenocarcinomas often take a papilliferous form, with the formation of papillary processes in the glandular spaces (Fig. 418). I have seen a tumor closely mimic a hypernephroma, and these hypernephroid tumors have been de-



FIG. 417.—Carcinoma of thyroid, medullary form. Sheets of cells surround acini containing colloid.  $\times 375$ .



FIG. 418.—Carcinoma of the thyroid. Papillary processes project into large spaces. There is no colloid.  $\times 175$ .

scribed by other writers. Different parts of the tumor may vary considerably in structure, and in places the picture may be practically that of the normal or slightly hyperplastic thyroid. Invasion of the veins occurs early and accounts for the early occurrence of distant metastases. The presence of tumor cells within the lumen of a vein is not of the great diagnostic value it was formerly thought to be. The distinction between benign and malignant hyperplasia is sometimes very difficult.

*Metastases* may occur early, owing to the marked tendency which the tumor shows to invade the blood vessels. The lungs and the bones are the common sites of secondary growths. The condition known as "benign metastasizing goiter" was for years described in the textbooks; it is characterized by the occurrence of a bone tumor composed of more or less



normal thyroid tissue in association with what was supposed to be a colloid goiter. All of these cases are really examples of carcinoma, and definite evidence of malignant disease of the thyroid will appear in due time.

**LATERAL ABERRANT THYROID TUMORS.**—These not uncommon tumors form a very distinct pathological and clinical entity. Although, as the name implies, it used to be thought that these tumors arose from aberrant thyroid tissue, there is now evidence to justify the belief that they represent lymph node metastases from a small slowly growing thyroid carcinoma of low malignancy. Many cases survive for long periods, despite the fact that the primary site has not been excised. The tumor, usually in a young person, is situated in the anterior triangle of the neck. It is well circumscribed and of slow growth. *Microscopically* its chief characteristic is its adenomatous and often cystic form and the presence of papillary processes. It is a papillary adenocarcinoma.

**HÜRTLE-CELL TUMOR.**—This is an adenoma the cells of which bear a striking resemblance to those of the liver, for they are large, polyhedral, with abundant strongly acidophilic cytoplasm, and arranged in trabeculae or small acini (Fig. 419). The lesion is usually benign, but may be malignant (adenocarcinoma); in the latter case the cells show the usual malignant characteristics. In 1894 Hürthle described a large acidophilic cell on the outer surface of the wall of the follicles, and the tumor was supposed to arise from these cells, but it is more probable that the acidophilic character of the cells signifies a functional change such as often occurs in the normal thyroid, and that they are not separate anatomical structures. The term *Langhans' tumor* (wuchernde Struma) occurs frequently in European literature. It is difficult to be certain of the identity of this lesion, but it seems to bear a close resemblance to the Hürthle-cell tumor, although usually markedly invasive.

**SECONDARY TUMORS.**—Secondary tumors of the thyroid are rare, with the exception of melanoma and carcinoma of the lung.



FIG. 419.—Hürthle-cell adenoma.  
X 240.

## INFLAMMATION OF THE THYROID GLAND

The subject of inflammation of the thyroid is one of extreme difficulty and at the present time it is not possible to give a clear and rational account of the process. A *subacute thyroiditis* has been described, which may have an acute onset with fever, a high sedimentation rate, and severe local pain and tenderness, or may be more chronic in type. It is a disease of early adult life. The thyroid is tender, firm, and symmetrically enlarged.

There is a dramatic response to Roentgen therapy, with prompt and complete relief (Crile and Rumsey). The cause is unknown, although infection by a virus has been suggested.

**Chronic Thyroiditis.**—The really puzzling group is that which includes the conditions known as Riedel's and Hashimoto's struma (an old name for goiter). Endless controversy has raged as to the relationship of these two forms of goiter, one group giving weighty evidence that they are distinct and separate entities, the other group producing even weightier evidence that Riedel's struma is the end product of Hashimoto's disease. The former view is championed by Joll, the latter by Levitt, both working on similar material from the same city (London). It is of interest to note, as pointed out by Levitt, that Riedel in the years between 1896 and 1910 described

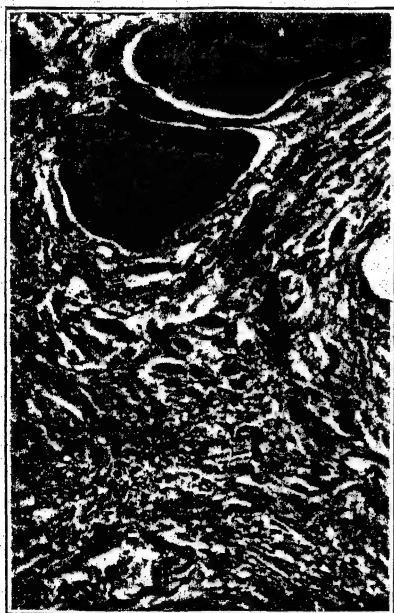


FIG. 420.—Riedel's struma.  $\times 120$ .



FIG. 421.—Hashimoto's struma, showing diffuse infiltration with lymphocytes.  $\times 250$ .

only three cases, of which the first alone was a true fibrosis, the others belonging to the group of subacute thyroiditis described above, whilst Hashimoto described four cases, only two of which by his own admission were typical, the fourth being characteristic of the Riedel group.

*Hashimoto's struma*, also known as *lymphadenoid goiter*, is the commoner of the two conditions, and occurs much more often in women. The thyroid is considerably and uniformly enlarged, moderately firm, but not adherent. Microscopically the acini are atrophic, but the characteristic feature is the abundance of lymphoid tissue, the cells of which may be arranged

diffusely or collected into follicles with germinal centers (Fig. 420). There may be a varying degree of fibrosis, a point to be remembered later.

*Riedel's struma* is also known as woody, or iron-hard thyroiditis, terms which indicate the extreme hardness of the gland. The female sex incidence is not so striking as in Hashimoto's disease. The hard thyroid is less enlarged than in the other struma, is of a whitish color, and merges with the surrounding tissues to which it is firmly adherent. It is, therefore, readily mistaken for carcinoma. Microscopically there is a degeneration of acini and a varying degree of lymphocytic infiltration, but the outstanding feature is the formation of dense sclerotic fibrous tissue (Fig. 421). Fragments of colloid may be surrounded by clusters of epithelial cells so as to give an appearance of giant cells. If these pseudogiant cells are numerous the lesion may be mistaken for tuberculosis. Both forms of struma may result in a clinical picture of myxedema.

As already indicated, the relationship of the two forms is the real problem, with which also is involved the nature of the lesions. Levitt has made a synthesis of the known facts which appears reasonable. There are three normal constituents of the thyroid, namely, epithelium, lymphocytes and fibrous tissue. As the acinar epithelium degenerates the lymphoid elements increase, but they diminish in number if fibrosis occurs. It is the opinion of Levitt and others that a definite series of steps may be traced from a degenerating toxic goiter through acinar degeneration, lymphoid hyperplasia to final fibrosis. In this view Riedel's fibrosis is an advanced stage of Hashimoto's struma. The process may be arrested and retrogress before fibrosis has occurred, so that it is natural that Riedel's struma is the rarer of the two conditions.

The irritant responsible for both forms or stages of the disease is probably a chemical one due to what has been termed "colloid spillage," which may be compared with the "spilled milk" believed to be the causal agent in plasma cell mastitis, and the part played by bile salts in the production of cholecystitis. Hellwig and his associates have shown by means of supravital staining of fresh tissue and electronmicrography that the colloid in the follicles contains specific particles, probably phospholipids. When the thyroid of an experimental animal is stimulated by the pituitary thyrotropic hormone a change occurs in the composition of the colloid, as a result of which macrophages are attracted into the lumen where they ingest the colloid, becoming colloidophages, and then return to the interfollicular stroma. If they then disintegrate, the liberated colloid attracts lymphocytes in large numbers which give a picture of chronic thyroiditis. The process of colloidophagy can be seen not only in the animal given thyrotropic hormone, but also in Graves' disease and to a marked degree in lymphadenoid goiter in the human patient. Cells now known to be colloidophages used to be taken for follicular epithelial cells desquamated into the lumen. The electronmicroscope shows that colloid from cases of chronic thyroiditis is similar to that from follicles stimulated by the pituitary hormone, but different from that of the normal gland. In the last analysis it would appear that chronic thyroiditis may well be due to abnormal stimulation by the pituitary, as is true of Graves' disease and other forms of toxic goiter.

## OTHER LESIONS OF THE THYROID GLAND

**INFECTIVE GRANULOMAS.**—*Tuberculosis* of the thyroid gland is rare, the gland showing a remarkable resistance to this infection. Miliary tubercles may occur, but must be distinguished from the pseudotubercles of Riedel's struma, and from similar structures which are very occasionally seen in diffuse and nodular goiters. Large areas of caseation may be formed, but this is extremely rare. *Syphilis* may not uncommonly cause enlargement of the thyroid in the secondary stage. Tertiary gummata are very rare.

**CONGENITAL ANOMALIES.**—The thyroid may be absent. Normally the gland is developed as a downgrowth from the anterior wall of the pharynx, the stalk connecting it with the pharynx forming the *thyroglossal duct*, which at birth is represented only by the dimple of the foramen cecum at the posterior part of the tongue. Portions may be displaced during the course of development. A nodule at the base of the tongue may form a *lingual thyroid*. There may be small masses in the neck known as *accessory thyroids*, and pieces may be found at some distance from the normal position. A portion of the duct may remain unobliterated and form a *thyroglossal cyst*, which is recognized by always being in the middle line of the neck. Pieces of parathyroid or thymus may be embedded in the thyroid.

## ADDITIONAL READING

- Adenomas.** GRAHAM: Arch. Path., 1933, 15, 741. REINHOFF AND LEWIS: Arch. Surg., 1928, 16, 79. WOMACK AND COLE: Arch. Surg., 1932, 23, 466.
- Carcinoma.** CLUTE AND WARREN: Surg., Gynec. and Obst., 1935, 60, 861. DUNHILL: Brit. J. Surg., 1931, 19, 83. GRAHAM: Surg., Gynec. and Obst., 1924, 39, 781. LAHEY, *et al.*: Ann. Surg., 1940, 112, 977. VAUX: J. Path. and Bact., 1937, 44, 463.
- Chronic Thyroiditis.** CHESKY, DREESE AND HELLWIG: Surg., Gynec. and Obst., 1951, 93, 575. HELLWIG: Science, 1951, 113, 725. JOLL: Brit. J. Surg., 1939, 27, 351. LEVITT: Lancet, 1951, 2, 957; Ann. Roy. Coll. Surg. Eng., 1952, 10, 369.
- Chronic Thyrotoxic Myopathy.** McEACHERN AND ROSS: Brain, 1942, 65, 181. THORN AND EDER: Am. J. Med., 1946, 1, 583.
- Fetal Adenoma.** HERTZLER: Arch. Surg., 1928, 16, 1187.
- Geographic Pathology of Goiter.** HELLWIG: Surg., Gynec. and Obst., 1932, 55, 35.
- Goiter and Hyperthyroidism.** HELLWIG: Arch. Path., 1939, 28, 870.
- Graves' Constitution.** WARTHIN: Ann. Int. Med., 1928, 2, 553.
- Graves' Disease.** MEANS: Lancet, 1949, 2, 543.
- Hashimoto's Disease.** CLUTE, *et al.*: Arch. Surg., 1935, 31, 419. HELLWIG: Arch. Path., 1938, 25, 838. JOLL: Brit. J. Surg., 1939, 27, 351. VAUX: J. Path. and Bact., 1938, 46, 441.
- Hürthle-cell Tumor.** MARTIN AND ELKIN: Ann. Surg., 1939, 110, 169. WILENSKY AND KAUFMAN: Surg., Gynec. and Obst., 1938, 66, 1.
- Hyperparathyroidism and Renal Disease.** FRITZ AND BRINES: Am. J. Path., 1951, 27, 265.
- Lateral Aberrant Thyroid Tumors.** KING AND PEMBERTON: Surg., Gynec. and Obst., 1942, 74, 991. WARREN AND FELDMAN: Surg., Gynec. and Obst., 1949, 88, 31. WOZENCRAFT, *et al.*: Cancer, 1948, 1, 574.
- Liver in Graves' Disease.** BEAVER AND PEMBERTON: Ann. Int. Med., 1933, 7, 687. BOYCE: The Role of the Liver in Surgery, Baltimore, 1941. CAMERON AND KARUNARATNE: J. Path. and Bact., 1935, 41, 267. WELLER: Ann. Int. Med., 1933, 7, 543.
- Myxedema.** LANGE: Am. J. Med. Sci., 1944, 208, 5. MARINE: Arch. Path., 1939, 28, 65. MEANS, *et al.*: Tr. A. Am. Physicians, 1940, 55, 32.
- Riedel's Struma.** DeCOURCY: J. A. M. A., 1943, 123, 397. McCLINTOCK AND WRIGHT: Ann. Surg., 1937, 106, 11. SCHILLING: Surg., Gynec. and Obst., 1945, 81, 533.
- Subacute Thyroiditis.** CRILE AND RUMSEY: J. A. M. A., 1950, 142, 458.
- Thiouracil in Goiter.** HALPERT, *et al.*: Arch. Path., 1946, 41, 155.
- Thyroid Physiology.** MEANS: Am. J. Med. Sci., 1944, 207, 1.

## THE PARATHYROID GLANDS

**PATHOLOGICAL PHYSIOLOGY.**—The parathyroid glands regulate the level of the blood calcium; they determine the rate of movement from the great calcium depots, the bones, into the blood stream and tissues, and from thence out into the urine. The blood phosphorus tends to vary inversely with the blood calcium; as the one goes up the other goes down. Renal disease may cause retention of inorganic phosphorus; this tends to depress the calcium, and would do so were it not for increased function of the parathyroids and consequent hyperplasia. Just as renal lesions can influence the parathyroids, so also can parathyroid overactivity cause renal lesions. The pathological physiology of the gland may vary in the direction of hyperfunction or hypofunction. Pure hyperparathyroidism gives rise to generalized osteitis fibrosa; pure hypoparathyroidism gives rise to tetany.

The parathyroids are the most difficult organs in the body to find at autopsy, partly on account of their small size, partly because of their resemblance to lobules of fat. Excellent instructions for their demonstration will be found in the appendix to Gilmour's paper.

**HYPERPARATHYROIDISM.**—In 1925 Collip succeeded in preparing a powerful extract of the active principle of the parathyroids (parathormone). Its action is to remove calcium from the bones in large amount, and owing to this mobilization of calcium the bones become rarefied, the blood calcium rises, and there is a marked excretion of calcium and phosphorus in the urine. The decalcification of bone is followed by the formation of fibrous bone lesions. The muscles are hypotonic, for the tissues are flooded with the mobilized calcium, and the neuromuscular irritability is accordingly diminished. The pathological counterpart of experimental hyperparathyroidism is *generalized osteitis fibrosa cystica*, which is usually associated with tumor of the parathyroids. Multiple bone cysts may be formed. There is hypercalcemia and an increased excretion of calcium in the urine. As the phosphorus of the blood usually varies inversely with the calcium, it is low in this condition.

There is a relationship between the parathyroid and kidneys as well as between the parathyroid and bones. Moreover this relationship is a reciprocal one. Hyperparathyroidism causes metastatic calcification of renal tubules which may lead to renal insufficiency. Conversely, prolonged renal insufficiency due to chronic glomerulonephritis, etc., is often associated with marked secondary hyperplasia of the parathyroid, sometimes also with secondary osteitis fibrosa. It appears probable that the parathyroid hyperplasia is dependent in some way on phosphate retention by the kidneys, all the more so as a similar hyperplasia can be produced experimentally by the repeated injection of sodium phosphate.

**HYPOPARATHYROIDISM.**—The clinical manifestation of this condition is tetany. Tetany may be produced in a variety of ways, all of which are connected directly or remotely with the low calcium in the tissues. Pure parathyroid tetany is best seen when the parathyroids have been removed intentionally in animals or unintentionally in man in the course of an operation for goiter. There is a marked drop in the blood calcium and an increased excretion of calcium in the urine. The phosphorus of the blood is normal or raised. The tissues are depleted of calcium, and tetany develops owing to the increased neuromuscular irritability. This hyperexcitability is shown by twitching of the muscles and severe colonic spasms and convulsions. When the nerves are stimulated electrically and even when pressed upon the muscles may go into a persistent tetanic spasm.

## PARATHYROID TUMORS

These tumors have a geographical distribution which is worthy of note. Although always somewhat of a rarity, they are much commoner in the

North Atlantic States, Scandinavia and England than in Italy or France. There are far more cases in the eastern United States than in the central states. Wilder and Howell suggest that the difference is due to the absence of the ultra-violet light stimulus in gloomy and highly industrialized (smoky) countries, thus putting a strain on the parathyroids which stimulates them to tumor formation. The tumor is usually an adenoma, sometimes a carcinoma. The normal parathyroids are composed of oxyphil cells and basophil or chief cells. It is probable that the former are derived from the latter. The adenoma may be composed mainly of either of these types of cell. The cells are usually large and clear (water-clear or "wasserhelle" cells), presenting a vesiculated or ballooned appearance owing to their rich glycogen content, and arranged in cords or columns (Fig. 422). The

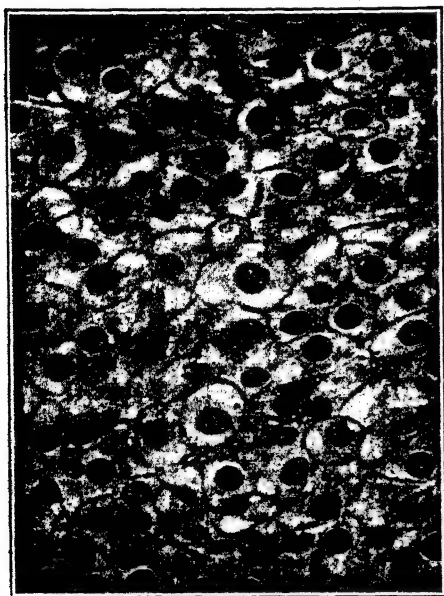


FIG. 422.—Parathyroid adenoma. The clear appearance of the cytoplasm is due to glycogen.  $\times 500$ .



FIG. 423.—Osteitis fibrosa. The extremely marked bony deformities are the result of hyperparathyroidism. (Ashhurs

tumor may be of considerable size, in one case weighing 60 grams. Although large it may lie so deep that it cannot be palpated even though it is suspected, as in a case described by Hunter and Turnbull, where the tumor measured 7.5 cm. and yet could not be felt. The other parathyroids atrophy on account of disuse. For this reason there may be a severe drop in blood calcium immediately following surgical removal of the adenoma, and the patient is in danger of developing tetany unless safeguarded with parathyroid extract. Acini containing colloid may be present and the stroma may be rarefied, so that it is easy to mistake the microscopic picture for that of a degenerating thyroid adenoma, especially if the tumor is embedded in the thyroid as sometimes happens. Occasionally there are bilateral tumors. Albright, together with Castleman and Mallory, describes

*hyperplasia* of the parathyroids rather than tumor in certain cases of hyperparathyroidism. All the parathyroids are diffusely enlarged, in contrast to the limited and localized enlargement of adenomas. The cells, which are of the water-clear variety, are extremely uniform in type, whereas in adenoma the cytological picture is usually more varied.

**SYMPTOMS.**—The symptoms of parathyroid tumors are those of hyperparathyroidism, and are similar to those produced by parathyroid extract. The bones are softened and rarefied, and the decalcification is readily recognized in the roentgen-ray picture. The softened bones become greatly deformed, the legs are bent, the pelvis wedge-shaped, and there is scoliosis and loss of height (Fig. 423). Multiple tumor-like swellings of the bone are common. These show the structure of a giant-cell tumor, the giant cells probably representing a foreign-body reaction to the disintegration of bone. The bone becomes replaced by fibrous tissue, and multiple cyst formation is common. The calcium removed from the bones appears in the blood, so that the blood calcium is raised from the normal 10 mg. per 100 cc. to 15 or 18 mg. The phosphorus is low, and this is a more valuable indication of hyperparathyroidism than is the raised calcium. In about half the cases, however, it returns to normal in the later stages, owing to renal failure to excrete phosphorus. The plasma alkaline phosphatase, an enzyme capable of splitting certain inorganic phosphates, is considerably raised. As the tissues are rich in calcium the muscles are hypotonic, having a low electrical excitability, and there is great muscular weakness. Large quantities of calcium are excreted in the urine, so that there is a negative calcium balance which is at once rectified when the tumor is removed. The calcium is deposited in the arteries, and in the renal pelvis in the form of calcium stones. There is often a fine spotty calcification of the renal tubules.

The classical picture of *osteitis fibrosa cystica* is rare and easy to recognize. Other slighter and less typical manifestations of hyperparathyroidism are much more common. The condition should be suspected in every case of renal calculus. The calculus cases due to parathyroid tumor are more often not associated with bone disease than with it. The replacement of the marrow by fibrous tissue may lead to anemia and leucopenia. Bone pain and tenderness may be present for a long time before deformities appear. Multiple myeloma and metastatic carcinoma in the skeleton may give a similar picture of decalcification of bone with high blood calcium, but the blood phosphorus is also high, thus distinguishing the condition from hyperparathyroidism. In one of my cases of secondary carcinoma of bone the blood calcium was above 18 mg. per 100 cc. Senile osteoporosis is the most difficult condition to differentiate from mild hyperparathyroidism.

**OTHER PARATHYROID LESIONS.**—Many other lesions of the parathyroid glands have been reported, but none of them appears to be of any importance. Hemorrhage may occur into the parathyroids of the child during labor, but enough tissue is left to perform the normal function of the glands. Even when all four parathyroids have been destroyed by secondary carcinoma, there have been no symptoms of tetany. Fibrosis and scarring is often found in elderly persons. Cysts are not uncommon. In none of these cases is there any evidence of functional disturbance.

#### ADDITIONAL READING

- General References.** SCHELLING: *The Parathyroids in Health and in Disease*, St. Louis, 1935.  
**Gross Anatomy of Parathyroid Glands.** GILMOUR: *J. Path. and Bact.*, 1938, 46, 133.

**Hyperparathyroidism and Renal Disease.** ALBRIGHT, *et. al.*: J. A. M. A., 1934, 102, 1276. ANDERSON: Arch. Path., 1939, 27, 753. CASTLEMAN AND MALLORY: Am. J. Path., 1935, 11, 1; 1937, 13, 553. HIGHMAN AND HAMILTON: Arch. Path., 1938, 26, 1029. HUNTER AND TURNBULL: Brit. J. Surg., 1931, 19, 203. JAFFE: Arch. Path., 1933, 16, 63. MCJUNKIN, *et. al.*: Am. J. Path., 1937, 13, 325. PAPPENHEIMER AND WILENS: Am. J. Path., 1935, 11, 73.

**Normal History.** MORGAN: Arch. Path., 1936, 21, 10.

## THE PITUITARY GLAND

**GENERAL CONSIDERATIONS.**—"Here in this well-concealed spot, almost to be covered by a thumb-nail, lies the very mainspring of primitive existence, vegetative, emotional, reproductive." In these striking words Harvey Cushing describes the pituitary body, one of the smallest of the endocrines, but the master gland of the body. The pituitary consists of an anterior lobe and a posterior lobe. The anterior lobe is epithelial in structure, and is derived from Rathke's pouch, an up-growth from the pharynx. The stalk connecting it with the pharynx disappears, but epithelial rests may remain from which tumors may arise known as Rathke pouch tumors or craniopharyngiomas. The posterior lobe, of nervous structure, is developed from the floor of the third ventricle, and remains attached to the hypothalamic region of the brain by a stalk or infundibulum, in which a very narrow channel of communication with the ventricle remains open. The posterior lobe consists of a pars nervosa and a pars intermedia. The pars nervosa consists of non-medullated nerve fibers, which connect the pituitary with the hypothalamus, and a varying amount of nerve cells and neuroglia. The pars intermedia is an epithelial investment of the pars nervosa, derived from Rathke's pouch. It is composed of basophil cells. The active principle of the posterior lobe may be derived in part from the cells of the pars intermedia.

The *anterior lobe* contains three types of cell (Plate XXII): (1) Acidophil or eosinophil cells, with granules staining red with eosin. These cells seem to govern the growth of the body. (2) Basophil cells, with granules staining with hematoxylin. These cells are perhaps concerned with sexual development, but of this there is no definite proof. The eosinophil and basophil cells are classed together as chromophil cells. (3) Chromophobe cells with non-granular cytoplasm which stains faintly. To bring out the differences in color it is well to use special stains. The proportion of the various forms is roughly as follows: chromophobe, 50 per cent; acidophil (eosinophil), 40 per cent; basophil, 10 per cent. The proportion of cells varies greatly in different sections from the same gland, so that it is difficult to speak of a normal picture; serial sections are really necessary to determine with accuracy the predominant cell. Moreover it is probable that the proportion is constantly changing. Studies on the Golgi apparatus suggest that there are only two fundamental cells, acidophil and basophil, both of which arise from chromophobes (Severinghaus). The chromophobes are of two types which can be distinguished by their Golgi apparatus; one of these develops into an acidophil, the other into a basophil. The pituitary becomes enlarged during pregnancy, and it is heavier in multiparæ than in nulliparæ and males.

This is no place for an account of the infinitely complex subject of the physiology of the pituitary. The anterior lobe, being glandular in structure, is the active part and is one of the most important organs in the body. It governs connective tissue growth, in particular that of bones, mental development, and the development of the reproductive organs. Being the conductor of the glandular orchestra it influences all the other endocrines, in particular the adrenals, thyroid and islets of Langerhans.



## PLATE XXII



Normal Pituitary Gland.

The acidophil (eosinophil), basophil and chromophobe cells are present in normal proportions. (Acid fuchsin and methylene blue.)

The cells of the pars intermedia, which appear to provide the active principle of the posterior lobe, become basophilic when ripe, are cast off, and invade the pars nervosa where they are changed into hyaline bodies which pass through the loose neural spaces to the infundibulum. This "basophilic invasion of the posterior lobe" becomes more prominent with advancing years.

Posterior lobe extract, known as pituitrin, contains several hormones, of which the most important are the vasoconstrictor, the oxytocic and the antidiuretic. The vasoconstrictor effect is part of a general contraction of plain muscle throughout the body, the oxytocic effect (*oxus*, quick; *tokos*, birth) is a contraction of uterine muscle, and the antidiuretic effect is on the epithelium of the renal tubules resulting in increased absorption of water, which is of value in the treatment of diabetes insipidus.

An intimate relationship exists between the pituitary and the hypothalamic centers of the diencephalon, which is the most ancient part of the cerebrum and has remained almost unchanged in the course of development. It governs the primitive functions such as sleep and water balance, and the primitive sensations such as hunger and thirst. Hypothalamic tumors and tumors pressing on the hypothalamus may give rise to such symptoms as polyuria, adiposity and pathological somnolence.

**HYPERPITUITARISM.**—With this brief review of the perplexing but all-important subject of pituitary structure and function we may endeavor to outline some of the clinical features of underactivity and overactivity of the gland and to determine the lesions which may give rise to this alteration of function. In discussing these clinical features it must be borne in mind that the cause of the disturbance of function is often a tumor, an adenoma, and that this tumor in addition to elaborating an excess of the hormone normally produced by its cells of origin will usually destroy the other types of cell. Even in the purest forms of hyperpituitarism we shall not expect to find an exaggeration of all the normal functions of the gland. There will nearly always be some insufficiency to mar the perfect picture. The main effect of hyperpituitarism is excessive growth of the connective tissues and especially of the bones. If this occurs before ossification is completed the result is gigantism; if after that process is completed, the result is acromegaly.

*Gigantism* is always due to pituitary hyperplasia. A definite tumor is usually present with enlargement of the sella turcica, but in the milder forms there may merely be hyperplasia of the anterior lobe. Associated with the skeletal overgrowth there may be a later development of symptoms of pituitary insufficiency, especially impotence in men and amenorrhea in women. The skeletal overgrowth is caused by hyperplasia of the eosinophil cells of the anterior lobe, while the subsequent sexual insufficiency is due to pressure on the cells of that lobe which are concerned with sexual stimulation (probably basophil cells). The pituitary activity may inhibit the action of insulin so that glycosuria develops, and it is common for giants to die with symptoms of diabetes. Later in the disease the tumor may be converted into a cyst so that the pituitary is greatly shrunken, but the skeletal changes are permanent, and the expanded sella bears witness to the former size of the gland.

*Acromegaly* is the result of hyperpituitarism after ossification is completed. The chief changes are enlargement of the bones, hypertrophy of

the connective tissue, and changes in the skin and hair, to which may be added later in the disease symptoms suggestive of hypopituitarism such as depression of the sexual function. The tumor found at operation or autopsy is more often a chromophobe than an acidophil adenoma, but it is probable that the cells were acidophil in the early phase of the disease. It was Pierre Marie who, in 1886, recognized the pituitary origin of the disease and named it from the great enlargement of the hands and feet (*akros*, extremity; *megale*, large). The face is large, the frontal sinuses prominent, the eyes deeply set, the lower jaw is heavily undershot and prognathous so that the lower teeth project beyond the upper ones, the teeth themselves are widely separated, the hands and feet are huge and clumsy with exostoses on the phalanges and a characteristic tufting of the terminal phalanx seen in the roentgen-ray picture. Kyphosis may be marked, and the patient with his bent back, huge hands reaching to the knees and protruding lower jaw presents a gorilla-like picture. In addition to the osseous changes there is marked connective-tissue hyperplasia which produces enlargement of the lips, tongue, nose, hands, and feet. Owing to this fibrosis the skin becomes thick, coarse, and furrowed, a change that is most strikingly evident in the scalp which is deeply corrugated like that of a bulldog. There is marked increase in the hair, which is thick and coarse, and profuse sweating is common. In the active stage of the disease there may be increased sexual excitement. Lactation after pregnancy may continue for a number of years. Changes in the basal metabolic rate are not constant, but during the active stage it may be increased and the appetite is sometimes voracious. Glycosuria occurs in about 20 per cent of the cases, but it is curiously inconstant in the same patient. The disease is self-limited, and the signs of overactivity become replaced by those of hypopituitarism, *i. e.*, adiposity, somnolence, and sexual impotence. The structural changes (bone and connective tissue) are of course permanent.

**HYPOPITUITARISM.**—This is a much commoner condition than hyperpituitarism, but the clinical manifestations are more varied and confusing, and the lesions to which the deficiency of pituitary secretion may be due are correspondingly varied. Three fairly well-defined types may be recognized, named respectively the *Fröhlich type*, the *Simmonds' type*, and the *Lorain type*.

1. The *Fröhlich syndrome*, which is the common form, is a dystrophia adiposo-genitalis that commonly develops about the time of puberty, but may appear later in life. Depression of the sexual function is the earliest and most constant symptom. There is amenorrhea in the female, due to absence of the hormone which stimulates ovarian function, and loss of libido in the male. The sexual organs remain undeveloped or atrophy. Of equal importance is atrophy of the skin and hair, in striking contrast to what is found in acromegaly. The skin is thin, delicate, smooth like a child's and dry. This is due to atrophy of the dermal connective tissue. The hair of the head is normal in amount but soft and fine; the facial, axillary and pubic hair is scanty; the skin of the trunk and legs is hairless. After the age of thirty-five years the soft skin becomes finely wrinkled owing to the lack of fibrous tissue in the dermis. Adiposity may be very marked or may be absent. When the condition develops in an adult male,

deposits of fat in the breasts, hip, buttocks, and lower abdomen give the figure a distinctly feminine cast. Sudden fluctuations of weight are characteristic. The basal metabolic rate is usually low. Mental dulness of varying degree is common. Sugar tolerance is not really high as is commonly supposed, for after the administration of glucose the blood-sugar curve takes an unusually long time to return to normal owing to the general slowing up of metabolic processes, but glycosuria never occurs, so that in that sense the patient has a good sugar tolerance. A variation of this syndrome is the adipose type, illustrated to perfection by the Fat Boy in *Pickwick*. His face is round and chubby, his mind is slow, and he is ready to drop asleep at a moment's notice.

Another rare and remarkable variation of the Fröhlich type is known as the *Laurence-Biedl syndrome*. This is characterized by a strong familial tendency, adiposity, genital dystrophy, mental deficiency, retinitis pigmentosa, and polydactylism. A patient with adiposity, partial blindness, and six fingers or six toes is easily recognized as belonging to this group, especially when it is found that other members of the family present the same condition.

2. The *Simmonds syndrome* may develop in adult life or in childhood. Both are examples of premature senility or *progeria*. When the disease appears in childhood the patient remains a dwarf. A person suffering from pituitary old age presents a remarkable clinical picture, for a child of ten may have the aspect of a decrepit old man. There is a general microsplanchnia, all the organs being small and underweight in contrast to the large heavy organs of acromegaly. The atrophy may affect the thyroid causing thyroid insufficiency (myxedema), or the adrenals causing adrenal insufficiency. The structure of the anterior pituitary is wiped out. Simmonds attributed this to embolism, but the blood reaches the anterior lobe by many channels, and there was no good evidence of the presence of emboli in his cases. Sheehan pointed out that extensive necrosis of the anterior pituitary is not uncommon in women during delivery, and this he attributed to thrombosis of the pituitary vessels caused by collapse after severe hemorrhage. Plaut, in an excellent review of the subject, comes to the conclusion that there is no good ground for considering necrosis of the pituitary to be ischemic in origin, either embolic or thrombotic. He has found subtotal necrosis in 9 per cent of 149 autopsies on adult males, in none of which could the lesions be explained by embolic or thrombotic vascular occlusion. He considers that the extensive necrosis seen in post-partum cases represents an exaggerated degree of a process that takes place frequently during the last days of life. It is possible that the necrosis may be anoxic rather than ischemic, owing partly to the high metabolic rate which is known to exist at least in the rat's pituitary during parturition, and partly to pressure of the sella on the enlarged pituitary of pregnancy. In the non-parturient cases the anoxia may be due to the circulatory failure which so often precedes death.

3. In the *Lorain type* the patient is bright mentally, but remains small and undeveloped sexually. When he grows up he remains like a graceful and attractive child. Peter Pan might be placed in this group. This type may be called pituitary dwarfism, just as the Simmonds' type may be called pituitary senility.

The lesions in hypopituitarism are varied. The usual organic cause is craniopharyngioma. Such tumors press upon the hypothalamus as well as upon the pituitary, and as they are congenital in origin and usually develop early in life, they cause some of the most extreme forms of adiposogenital dystrophy in children. Chromophobe adenoma of the pituitary

may sometimes be responsible. This seldom develops before the age of twenty years, and therefore fails to explain the cases occurring in childhood. As the adenoma is often confined to the sella and therefore may not press on the hypothalamus, adiposity may be slight or absent. A much rarer group is that of pituitary necrosis (Simmonds). Many of these cases of pituitary old age have been attributed to puerperal sepsis. In other cases nothing is found beyond a hypoplasia of the pituitary, which is indicated clinically by the very small size of the sella turcica. In addition to these gross organic causes there can be little doubt that in the majority of cases there is no tumor or necrosis, but merely a hypofunction of the gland, often temporary in character, as a result of which there may be some retardation of growth, lack of sexual development, or undue adiposity, all of which may be remedied in the course of a few years.

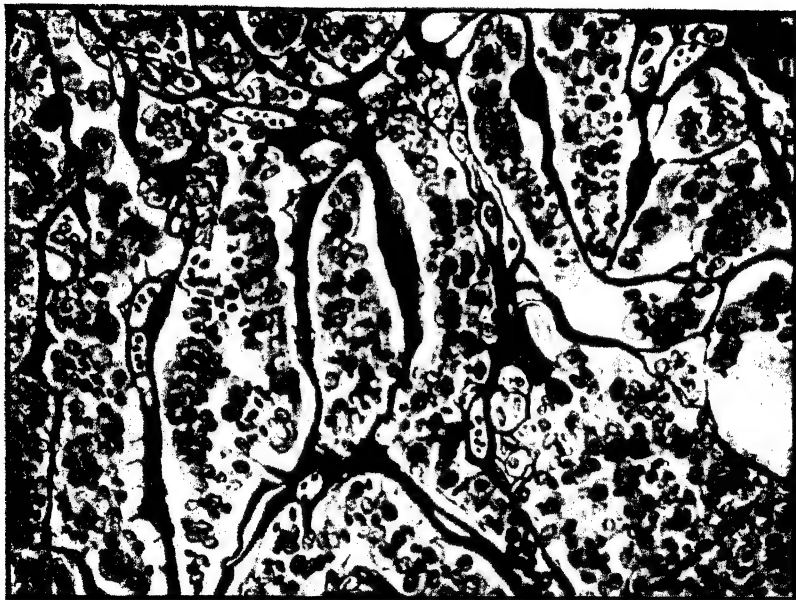
### TUMORS OF THE PITUITARY GLAND

A tumor of the pituitary is an adenoma, usually innocent, rarely a malignant adenoma. It may be debated whether the common adenoma is a true tumor or merely a glandular hyperplasia, but from the practical standpoint it must be regarded as a tumor, the most serious effect of which is often the pressure which it produces. Pituitary adenomas may be divided into three types: (1) chromophobe, (2) acidophil, and (3) basophil.

**Chromophobe Adenoma.**—This is much the commonest form of pituitary tumor. The chromophobe cells are non-granular, so that the cells of the tumor appear clear. Most of these tumors show a very characteristic alveolar grouping, with fibrous septa between the groups (Plate XXIII), but in some the cells are arranged diffusely. The type of tumor can usually be recognized by this alveolar arrangement without having recourse to a special study of the granules. The tumors about to be described are those which produce symptoms either local or general. Much more common are collections of cells which have been called subclinical adenomas (Costello), usually miliary or microscopic in size and producing no symptoms. The cell pattern differs from the normal and may be that of a convoluted papilloma or a compound tubular gland. These cell collections are not encapsulated. When symptoms are present they are those of pituitary insufficiency, similar to the changes produced in an animal when the anterior lobe is removed. Chromophobe cells are parent cells of eosinophils and basophils, and their overgrowth apparently gives rise to no positive symptoms. The negative symptoms of insufficiency are the result of compression of the more actively functioning eosinophil and basophil cells. The adenoma often remains confined to the sella, causing interference with skeletal and sexual development. If it breaks through the membranous roof and presses on the tuber cinereum, hypothalamic adiposity will be superadded.

**Acidophil Adenoma.**—The eosinophil adenoma is a good deal less common. It is composed of cells filled with red-staining granules (Plate XXIV), the cells are large and often multinucleated, and they are arranged diffusely, with complete absence of the alveolar grouping so characteristic of the chromophobe adenoma. The eosinophil cells are concerned

## PLATE XXIII



### Chromophobe Adenoma of Pituitary.

The pale cells show a definite alveolar grouping. Four acidophil cells are present.  
(Mann's stain).

with skeletal growth, so that the tumor is associated with the syndrome of overgrowth, *i. e.*, gigantism or acromegaly. The acidophil adenoma may give rise to the nearest approach to pure hyperpituitarism (skeletal overgrowth, connective-tissue hyperplasia, hypertrichosis, glycosuria, increased metabolic rate), but later in the disease insufficiency symptoms become apparent. It has already been remarked that the tumor found at autopsy is often a chromophobe adenoma, but it is probable that it was acidophilic in type in the earlier phase of the disease.

**BASOPHIL ADENOMA.**—This is by far the rarest form of adenoma associated with symptoms, although minute examples are not an uncommon incidental finding at autopsy. Cushing thought that the syndrome which goes by his name was caused by this tumor, but it is now evident that the lesion is only secondary, an effect rather than a cause. The constant lesion in Cushing's syndrome is hyalinization of the basophil cells with disappearance of their granules first described by Crooke. Hyalinization is an indication of inactivity of the basophils, and the occurrence of small basophil adenomas may indicate merely an attempt to compensate for the depressed basophil function.

Heinbecker, in an excellent review of the subject, points out that at least three primary lesions may be precursors of the all-important hyalinization of the basophil cells; these are (1) a tumor of the adrenal cortex, (2) a tumor of the thymus, and (3) atrophy of the nuclei of the hypothalamus. Experimental lesions of the hypothalamus in the dog are followed by marked loss of basophil cells with degenerative changes in the remaining basophils. The most frequent primary lesion is a tumor (usually a benign adenoma) or hyperplasia of the adrenal cortex. Every case of Cushing's syndrome should therefore be explored for adrenal tumor.

**MALIGNANT ADENOMA.**—This is a rare condition. In Cushing's series there were only 3 malignant tumors compared with 159 innocent ones. The tumor destroys the base of the skull, bursts through the roof of the sella, and invades the floor of the third ventricle. The cells, which are of the chromophobe type, are grouped in irregular masses.

**Neighborhood Symptoms.**—The effects of a pituitary tumor may be divided into general tumor symptoms, endocrine symptoms, and neighborhood symptoms. The first group comprises the symptoms of cerebral tumor in general, particularly increased intracranial pressure. If the tumor is small and confined to the sella these symptoms will be absent. The endocrine symptoms have already been discussed. The neighborhood symptoms are caused by pressure on neighboring structures. Pressure on the optic nerve causes optic atrophy of the primary type. The most characteristic pressure symptom is bitemporal hemianopsia due to compression of the inner fibers of the optic chiasma. There may be pressure on the hypothalamus with production of the hypothalamic syndrome (adiposity, polyuria). This is more likely to be caused by a chromophobe than a chromophil adenoma, as the latter remains confined to the sella long after the development of symptoms of hyperpituitarism. The sella is always expanded by the tumor, and may be markedly ballooned, with absorption of the clinoid processes.

**Craniopharyngiomas.**—Tumors of Rathke's pharyngeal pouch or the hypophyseal duct, conveniently called craniopharyngeal tumors, arise from vestigial remnants of the epithelial tract from which the anterior lobe of the pituitary is originally formed. They are usually suprasellar

tumors, but may originate and be confined within the sella. They may be quite minute, about the size of a pea, or may form huge calcareous masses as large as a tennis ball. The tumor usually appears under the age of fifteen years, and attains a much larger size than the average pituitary adenoma. Cystic degeneration and calcification of the wall of the cyst are common, and suprasellar calcification (x-ray) is a clinical sign of great value. The tumor may compress the pituitary, causing retardation of growth, but the most marked symptom may be adiposity due to pressure on the hypothalamus. The most typical form of Fröhlich's syndrome in tumors is produced by Rathke pouch tumors. Microscopically the tumor is usually an epidermoid carcinoma, but it may be a basal-cell cancer of the adamantinoma type. Cystic degeneration is common, and the entire tumor may be converted into a cyst.

**DERMOID TUMORS.**—Dermoid tumors are of rare occurrence in this region. They are due to invagination of the cranial epidermis during closure of the neural canal.

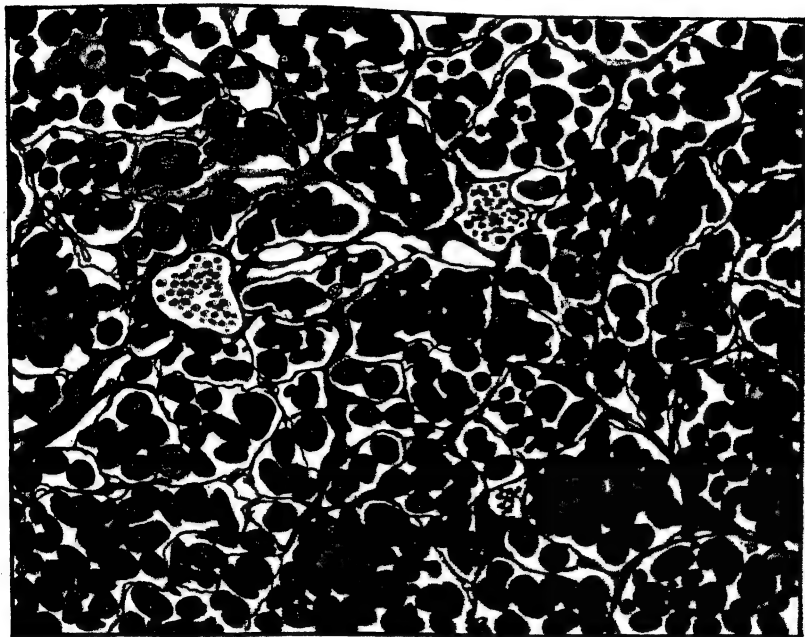
**CONGENITAL ANOMALIES.**—The anterior lobe of the pituitary is formed from a diverticulum from the roof of the buccopharyngeal junction. A remnant of this process is practically constant under the pharyngeal mucosa, where it is known as the pharyngeal hypophysis. Other remnants may be left along the course of the craniopharyngeal canal where they may give rise to the craniopharyngiomas. Congenital hypoplasia of the gland is found in various types of dwarf.

#### ADDITIONAL READING

- Basophil Adenoma.** CUSHING: Bull. Johns Hopkins Hosp., 1932, 50, 137. CROOKE: J. Path. and Bact., 1935, 41, 339.
- Cushing's Syndrome.** CROOKE: J. Path. and Bact., 1935, 41, 339. CROOKE AND CALLOW: Quart. J. Med., 1939, 8, 233. HEINBECKER: Medicine, 1944, 23, 225.
- Cytology.** RASMUSSEN: Am. J. Path., 1933, 9, 459.
- Pituitary and Hypothalamus.** POPJÁK: J. Path. and Bact., 1940, 51, 83.
- Pituitary Tumors.** CUSHING: Bull. Johns Hopkins Hosp., 1932, 50, 137. DOTT AND BAILEY: Brit. J. Surg., 1925, 13, 314. KRAUS: Arch. Path., 1945, 39, 343.
- Simmonds' Disease.** PLAUT: Am. J. Path., 1952, 28, 883. SHEEHAN: J. Path. and Bact., 1937, 45, 189; Quart. J. Med., 1939, 8, 277.



## PLATE XXIV



### Eosinophil (Acidophil) Adenoma Pituitary.

The cytoplasm of the cells is intensely red compared with that of the red blood cells in the capillaries. The arrangement is much more diffuse than in the chromophobe adenoma.

## Chapter

## 29

# THE LYMPHOID STRUCTURES

## THE SPLEEN

**DESCRIPTIVE OUTLINE.**—In describing the spleen consider the size, weight, color, consistence, and cut surface. The *size* varies much within normal limits, depending on age, physiological state, etc. The average length is about 12 cm., the breadth 7 cm., and the thickness 3 cm. In old age the spleen becomes atrophic, and the shrinking of the organ leads to wrinkling of the capsule which is also thickened. The *weight* is 150 to 200 grams. The *color* is a reddish-purple. The *consistence* is pliable (not really soft) and somewhat friable. On the *cut surface* the fibrous trabeculae are seen as thin white lines, and the Malpighian bodies as pale gray spots about 1 mm. in diameter. In the senile spleen the fibrous framework is greatly increased. The microscopic study of the spleen is difficult for the student and also for the expert. The picture is confused and nothing appears to be clean cut. It will help if attention is paid to the following: (1) lymph follicles (Malpighian bodies) together with the arterioles which they surround, (2) pulp, (3) sinusoids, and (4) trabeculae. The arterioles frequently show a hyaline thickening, especially with advancing years; this is of less pathological significance in the spleen than in any other organ. The sinusoids can hardly be seen in health; in disease they may be dilated and the lining cells become prominent. The normal trabeculae are often mistaken by the student for pathological fibrosis.

**PHYSIOLOGY.**—It is usual to regard the spleen as a great reticulo-endothelial sponge with a supporting framework of trabeculae and reticulum and a certain amount of lymphoid tissue superadded. Such a structure is designed to detain and alter the blood which slowly percolates through it. When the blood has traversed the arterioles it flows out into the wide marsh of the splenic pulp, from which it is collected into venous sinusoids. The walls of these sinusoids are fenestrated in a remarkable manner so that the cells wandering through the pulp may enter these venous channels in the freest manner. The effect of the whole arrangement is to bring the cells of the blood into the most intimate contact with the elements of the reticulo-endothelial sponge.

A rather different conception of splenic physiology is afforded by Knisely's direct microscopic observations of living transilluminated mammalian spleen. By this technique the sinusoids appear to be separated by partitions of pulp and lined by walls which are readily permeable to fluid and colloids but not to red blood cells. There seems to be a phase of storage of blood and a phase of flow, the flow being regulated by sphincters situated on the arterial and venous sides of the sinusoids. The cycle begins with closure of the sphincter on the venous side, as a result of which the sinus becomes

distended with blood and fluid passes through the wall into the pulp. When the sinus is completely distended with red cells the sphincter on the arterial side shuts, and the corpuscles lie free from plasma for a varying period, sometimes up to ten hours. The sphincter on the venous side then opens, and a soft mass of red cells passes into the vein. During the phase of storage or separation the erythrocyte-plasma interface is profoundly changed, as a result of which the cells become spherical instead of biconcave and are therefore more readily hemolyzed. The importance of these observations becomes evident when hemolytic anemia is considered. Knisely claims that many of the appearances seen in microscopic sections, such as infiltration of the pulp with red cells and slits in the sinus wall through which cells can pass, are due to rapid agonal changes.

The suggested *functions* of the spleen are varied. These are: (1) a filter for bacteria and worn-out erythrocytes; (2) a former of antibodies; (3) a manufacturer of blood in conditions such as pernicious anemia and osteosclerotic anemia; (4) a reservoir or bank for red cells, undoubtedly true for certain animals, but doubtful in the case of man; (5) a storer of iron in the specific iron-protein compound ferritin.

### INFECTIONS OF THE SPLEEN

**Acute Splenitis.**—There is no organ which can so rapidly change its size as the spleen. The normal spleen weighs about 150 grams, but in acute infections it soon becomes two or three times that size. It is not likely to be palpable until it is about three times the normal size, especially if it is soft. This acute enlargement is often called acute splenic swelling or acute splenic tumor. The most striking examples are shown by what may be termed the *septic spleen*, which is seen in pneumonia, septicemia, acute endocarditis, and other acute infections. It is enlarged, often very soft, and of a grayish-pink color. The pulp swells up in a pouting fashion on the cut surface, and is so soft that it can be wiped away with the knife. The softest spleens are seen in septicemia and pyemia. The swelling is due partly to enormous numbers of cells trapped in the pathless forest of the pulp, partly to local proliferation. Rich and his associates have shown by motion picture studies of tissue cultures that the large, basophilic, mononuclear cells which predominate have the same method of locomotion as lymphocytes, and are therefore probably lymphoid in character. In *typhoid fever* the spleen is enlarged so as usually to be palpable, soft, and deep in red color. The cut surface may resemble red jelly. The splenic pulp and sinuses are crowded with red blood corpuscles, together with large numbers of the macrophages characteristic of typhoid infection. Many of the macrophages contain erythrocytes which have been phagocytosed. In diphtheria and other acute infections of childhood there may be marked swelling of the lymph follicles so that they become visible to the naked eye.

**TUBERCULOSIS.**—Tuberculosis of the spleen is of little importance. In general miliary tuberculosis the spleen is enlarged and may be studded with tubercles, which are easily mistaken for enlarged lymph follicles. Occasionally large caseous masses are scattered throughout the spleen causing marked enlargement of the organ. The primary lesion in the lung or lymph nodes may be so small and quies-

cent that it is readily overlooked, and the condition is described as primary tuberculosis of the spleen. A large solitary tubercle (tuberculoma) is of very rare occurrence.

**SYPHILIS.**—In congenital syphilis the spleen is frequently enlarged and contains large numbers of spirochetes. The condition is often associated with marked anemia.

**MALARIA.**—Enlargement of the spleen is one of the commonest lesions in malaria. In an acute attack the spleen is moderately enlarged and soft, but as a result of long-continued infection it becomes greatly enlarged and very hard (*ague-cake spleen*). In malarial districts the greater part of the population may have enlarged spleens, giving the children in particular a pot-bellied appearance.

**KALA-AZAR.**—Kala-azar is a common cause of splenomegaly in the tropics. The spleen is very greatly enlarged, fibrosis is marked, and the pulp is filled with macrophages containing the Leishman-Donovan parasites which have already been described in Chapter 8. The parasites are readily demonstrated by means of splenic puncture.

**AMYLOID.**—The splenic lesions have already been described in connection with amyloid disease (Chapter 2). The spleen is much enlarged, elastic, and very firm. The common lesions affect the arterioles of the lymph follicles, but the fibrous reticulum is sometimes involved. The disease is almost never confined to the spleen.

### CHRONIC SPLENOMEGALY

It is impossible to make any satisfactory classification of the chronic enlargements of the spleen, as so little is known regarding their real nature, but we may recognize disease conditions affecting the principal elements of which the organ is composed, *i. e.*, lesions of the vascular structures, the reticulo-endothelial structures, and the lymphoid structures. In the first group we have splenic anemia and infarction, the second group includes Gaucher's disease, Niemann-Pick's disease, hypercholesterolemic splenomegaly, and hemolytic jaundice, while in the third group there are the leukemias.

**Splenic Anemia.**—This is an example of what Eppinger calls hepato-splenic (hepato-lienal) fibrosis, an excellent term indicating that the liver and spleen form a unitary system either or both members of which may be the seat of unexplained fibrotic lesions. When the liver is principally affected the condition is called cirrhosis. When the main lesions are in the spleen the condition is called splenic anemia. *Banti's disease* is a name which has long been applied to those cases in which there is first enlargement of the spleen with anemia and leucopenia, followed later by cirrhosis of the liver with ascites and a tendency to gastric hemorrhage. This association is so variable and the clinical picture is so indefinite that little is to be gained by preserving the name. One may speak of the Banti syndrome, but it is certainly not a separate disease entity. The development of clinically evident cirrhosis of the liver in splenic anemia is an uncommon occurrence. Microscopic evidence of cirrhosis, however, can be found in 70 to 80 per cent of cases. The ordinary case displays a characteristic triad of symptoms, *i. e.*, splenomegaly, secondary anemia and leucopenia, and gastric hemorrhage.

The nature of the condition has long been a matter for discussion. Banti's view that the splenic condition was primary has become untenable, in

spite of the fact that removal of the spleen may sometimes cure the condition. This is true of other diseases where the changes in the spleen cannot be regarded as fundamental (hemolytic jaundice, thrombocytopenic purpura). Evidence is accumulating that splenic anemia is a vascular disturbance of the spleen due to high portal blood pressure. There is a valvular mechanism in the splenic arterioles at the point where they end in the ellipsoids, so that the back-pressure is not transmitted to the splenic artery, but makes its effects felt on the splenic pulp. The question of how much the spleen will enlarge depends a good deal on the age of the patient, marked enlargement occurring more readily in young persons. The cause of the

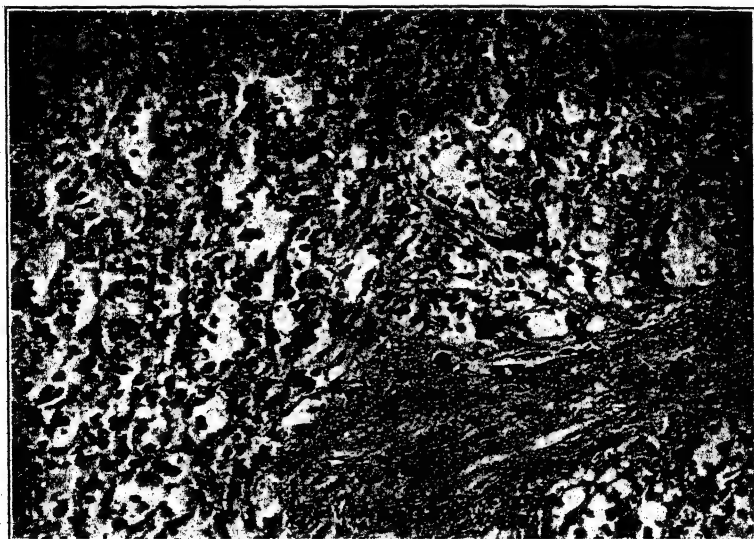


FIG. 424.—Banti's disease. General fibrous thickening of splenic reticulum and dilatation of the sinuses.  $\times 250$ .

portal hypertension is a matter of uncertainty; indeed it must be understood that the idea itself is still hypothetical. Cirrhosis of the liver is a sufficient cause, but splenomegaly usually develops long before there is any indication of cirrhosis. Measurements of the diameter of the branches of the portal vein in the liver show that there may be considerable narrowing with little or no cirrhosis in the ordinary sense of the word. Other causes of portal back-pressure are thrombosis of the portal or splenic veins, and vasodilatation of the hepatic artery. It is possible that in some cases the primary lesion may be in the spleen, a fibrosis of the Malpighian arterioles which are known to regulate the blood flow through the spleen. This would allow too much blood to enter the spleen, with resulting congestion and fibrosis. Finally, Dameshek's theory of hypersplenism offers a possible explanation for the blood picture, which may be a nonspecific reaction of the hemopoietic tissues to splenomegaly.

**LESIONS.**—The spleen is much enlarged and very firm. The average weight is 800 to 900 grams. The capsule is thickened, and the cut surface, from which no blood escapes, has a fibrosed or beefy appearance. The *microscopic lesions* are similar to the changes found in portal cirrhosis. The chief features are dilatation of the sinuses and thickening of the fibrous framework of the organ (Fig. 424). The fibrosis is periarterial in origin, extending throughout the reticulum, and finally involving the main trabeculae. The arteries usually show hyaline degeneration, but this change is of such common occurrence beyond the first decade that it has no special significance. Periarterial hemorrhages are frequent. A common finding is the presence of yellowish-brown flecks like flakes of tobacco leaf on the cut surface. Microscopically these may present a peculiar filamentous appearance, so that the lesions have been mistaken by

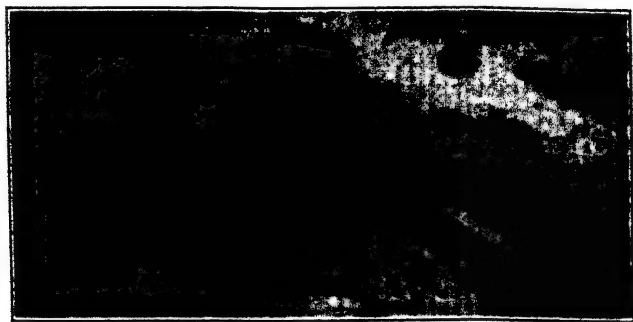


FIG. 425.—Siderotic nodule in spleen. The bamboo-shaped crystals are very characteristic.  $\times 1000$ .

some observers for the mycelia of fungi. The filaments are merely elastic fibers on which iron has been deposited, and the so-called fructification organs of the supposed fungi are pale green crystals jointed together like a bamboo cane. In addition to the filaments and crystals there are masses of hemosiderin, some of which is intracellular and some extracellular, together with giant cells and deposits of calcium. The whole mass gives an intense reaction for iron, and may be called a *siderotic nodule* (Fig. 425). These nodules are probably caused by hemorrhage at the point of termination of the arteriole in the ellipsoid where there is a valvular arrangement, so that raised portal blood pressure may cause rupture of the vessel at this point (McNee). The hemorrhage is followed by organization and fibrosis. Much of the iron-containing blood pigment is carried away by phagocytes, but some may be taken up by fibroblasts. These cells proliferate and lay down collagen fibers, and in this way the splenic reticulum becomes more and more fibrosed. All cases of splenic anemia do not show siderotic nodules, nor are the nodules confined to this disease. Their great importance lies in the fact that they indicate an increase in the portal blood pressure, which is the chief cause of the hemorrhages. The nodules are also found in the intensely congested spleen of hemolytic jaundice, in which hemorrhage may readily occur.

Degenerative changes in the splenic vein and portal vein are of common occurrence, and there may be thrombosis. These lesions are probably secondary to heightened portal blood pressure. If they are sufficiently great they may produce some of the splenic changes. Thickening of the wall (phlebosclerosis), endophlebitis, atheromatous change, and calcification are the chief lesions. The vein may be greatly distended, and huge collateral channels may connect the spleen with the stomach and diaphragm. The liver may or may not show cirrhosis of the portal type, but even when there is no cirrhosis it is probable that there is narrowing of the terminal branches of the portal vein.

**THE RELATION OF SYMPTOMS TO LESIONS.**—The enlargement of the spleen is probably the result of the increased portal pressure, which causes the dilatation of the sinuses, the hemorrhages, and indirectly the fibrosis. The gastric hemorrhage, one of the most constant and often one of the earliest of the symptoms, can best be explained by the same mechanism. These hemorrhages are analogous to the siderotic nodules in the spleen. In the former the blood escapes on a free surface, while in the latter it is imprisoned within a solid organ. The cause of the anemia is unknown. The anemia, usually associated with leucopenia, is not of the hemolytic type, for there is no evidence of undue hemolysis, and the fragility of the red cells is not increased. It may not develop until long after the splenomegaly has been detected, but it appears to be related to the lesions in the spleen, for splenectomy may cure the disease if it is not too far advanced. The gastric hemorrhages may contribute to the condition, but cannot account for all the cases. Possibly there is a condition of hypersplenism, as a result of which the erythrocytes are injured, but this is a pure guess. Indeed we cannot say for certain if there is such a thing as hypersplenism, though it appears probable. It must be remembered that in portal cirrhosis of the liver a progressive anemia is the rule. The three conditions which are most benefited by splenectomy are hemolytic jaundice, thrombocytopenic purpura, and splenic anemia.

**Infarction.**—An infarct of the spleen may be caused in the usual way by embolic occlusion of the artery. If the embolus is infected an abscess will be formed in the spleen. Or it may develop as the result of vascular disturbances in the spleen (thrombosis of the splenic vein) in such conditions as splenic anemia and leukemia, and injury to the organ, especially rupture. It presents the usual characters of an ischemic infarct, but in addition siderotic nodules may be present. The infarct reaches the surface and involves the surface, in contrast to infarct of the kidney where a thin rim of uninvolved tissue separates the infarct from the capsule. This explains why pain is a symptom more characteristic of splenic infarct than of renal infarct.

**Chronic Congestion.**—The spleen may become congested and enlarged either as the result of mitral valvular disease or of portal obstruction from cirrhosis of the liver. The enlargement in mitral disease is much less than in cirrhosis, because the liver serves to take up the back-pressure, only a small proportion of which reaches the spleen, so that the enlargement can seldom be detected clinically.

The *cardiac spleen* is about double the normal size (normal weight, 150 grams), dark, and very firm owing to a gradually increasing fibrosis. The sinuses are distended, the pulp infiltrated with red blood cells, and the

fibrous reticulum much increased. The lymphoid tissue tends to disappear. No siderotic nodules are found in this condition.

**Primary Reticulo-endothelial Granulomas.**—There exists a group of five rare diseases characterized by an accumulation of large pale reticulo-endothelial cells. These cells contain lipids varying in amount with the members of the group. Two of these reticuloses, Gaucher's disease and Niemann-Pick's disease, are lipid in character; there is a true disturbance of lipid metabolism associated with hyperlipemia. They are lipid-storage diseases or lipidoses. The other three, Schüller-Christian's disease, Letterer-Siwe's disease and eosinophilic granuloma of bone, are non-lipid reticuloses. As suggested by Farber they appear to be variants of the same basic disease disorder of the reticulo-endothelial system. Common to all three there are collections of large pale mononuclear cells, often phagocytic



FIG. 426.—Gaucher's disease.  $\times 315$ .

and containing lipid. Eosinophils are common to all three, but are most numerous in the earlier stage of eosinophilic granuloma, disappearing with the advancing age of the lesion and the conversion of the mononuclears into foam cells. The clinical variations seem to depend largely on the effect of age on the reactions (Demmis and Rosahn). The younger the age, the more acute and malignant the process. Lesions of the skin and the lymph nodes are common both to Letterer-Siwe's disease and Schüller-Christian's disease.

**Gaucher's Disease.**—This rare condition is a disorder of the reticulo-endothelial system. It commences in early life and is sometimes familial. Very exceptionally it appears to develop in the adult, when it runs a mild and prolonged course. There is an extreme degree of splenomegaly, moderate enlargement of the liver, some secondary anemia and rather pronounced leucopenia, a brownish-yellow coloration of the skin, and yellow wedge-shaped patches in the conjunctiva on each side of the cornea. Splenic puncture shows the very characteristic large, pale Gaucher cells. Roentgen-ray examination shows rarefaction of the bones, flattening of



the head of the femur, and a fusiform expansion of the lower end of that bone. As the vertebræ are involved in the rarefaction, the stature may be stunted.

The spleen may be enormous, filling the greater part of the abdomen. White spots are scattered over the surface, and these consist of very large, peculiarly pale cells filled with lipid (Fig. 426). These are the Gaucher cells, and represent the reticulo-endothelial cells of the organ filled with the cerebroside, kersin. The cerebroside is in the form of a lipoprotein. It stains feebly with the ordinary fat stains, but intensely with McManus' periodic acid-Schiff reaction and with Weigert's method designed for the more complex lipids. It is the swelling of these cells which causes the great enlargement of the spleen. The lesions are not confined to the spleen, but are found also in the liver, lymph nodes, bone-marrow, and other parts of the reticulo-endothelial system. The anemia and leucopenia are caused by the bone-marrow lesions. In one form of Gaucher's disease the lesions are mainly osseous. All the affected members of a family may suffer from this form. Pick mentions a family in which five brothers developed skeletal lesions. Scarcely a bone in the body may be spared. The disease is an example of lipid storage by the cells of the reticulo-endothelial system. The basis of the condition is a disturbance of lipid metabolism, the nature of which is at present unknown.

**NIEMANN-PICK'S DISEASE.**—This is an even rarer condition than Gaucher's disease, of which it may be regarded as a variation. It is a familial condition, occurring nearly always in Jewish infants, and the child does not live beyond the second year. In addition to involvement of the spleen, liver, lymph nodes and bone-marrow as in Gaucher's disease, the characteristic lipid-filled cells are found in the adrenal, pancreas, thymus, intestinal mucosa, lung, brain, and renal glomeruli. The affected cells are much more vacuolated than in Gaucher's disease. With the McManus stain the cells remain colorless, whereas Gaucher's disease cells stain rose-purple. The histiocytes as well as the endothelial and reticular cells are involved, so that it is a true lipid histiocytosis. Many epithelial cells may contain the lipid, *e.g.*, thyroid and kidney, and the monocytes of the blood may also be filled with this material. Widespread involvement of the ganglion cells of the brain and retina is the basis of amaurotic family idiocy. The lipid differs from that of Gaucher's disease in being a phospholipid, namely, sphingomyelin.

**LETTERER-SIWE'S DISEASE.**—This is a nonlipid reticulo-endotheliosis, but with many features in common with the lipid reticulo-endothelioses described above. It is a disease of infants and young children which runs a rapid and fatal course marked by a skin eruption, hepatomegaly, splenomegaly, lymphadenopathy and progressive anemia. There is universal proliferation of the reticulo-endothelial cells, with an increase in size of those organs containing large numbers of these cells. Few organs escape. The cellular proliferation is both diffuse and focal with the formation of nodules.

**SCHÜLLER-CHRISTIAN'S DISEASE.**—This very rare condition is characterized by defects in the membranous bones, especially the skull, exophthalmos, and diabetes insipidus—at first sight a curious mixture. The lesions are the result of accumulations of reticulo-endothelial cells which contain lipid (cholesterol) at some time in the disease. It seems to be a primary xanthomatosis often associated with giant-cell formation. The bone defects are due to erosion caused by periosteal deposits of xanthoma cells, the exophthalmos to deposits in the orbit, and the diabetes insipidus to deposits around the pituitary. The pituitary lesion may also cause

dwarfism. Almost any organ may be involved. Lesions in the lung may result in pulmonary fibrosis. The disease shows extreme variations in its course, the localization of the lesions and the clinical manifestations. It generally affects young adults, and may be very chronic in character, lasting for many years. In early childhood it is rapidly fatal.

**Hemolytic Jaundice.**—This condition is considered in connection with diseases of the blood, but brief reference may be made to the condition of the spleen. The spleen is moderately enlarged, deep red in color, and the pulp is filled with red blood cells to an incredible degree, so that all traces of splenic structure disappear unless the spleen is drained of blood before

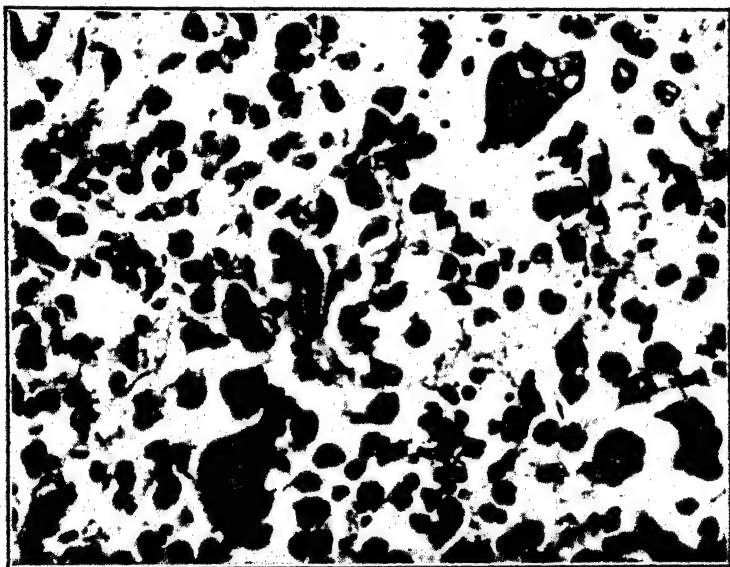


FIG. 427.—Myeloid metaplasia of spleen showing marrow-like picture and multinucleated giant cells.  $\times 610$ . (Boyd, Pathology of Internal Diseases.)

being fixed. When this is done it is seen that the sinuses are relatively empty. If the spleen is removed in the active stage of the disease it is found to contain a great amount of hemosiderin, for the most part within the reticulo-endothelial cells. During the inactive stage there is little or no pigment. In this disease there is evidently a great increase in the phagocytic activity of the reticulo-endothelial cells, although the essence of the condition is an increased fragility of the erythrocytes, and the splenic enlargement is due to hypertrophy of these phagocytic cells as well as to accumulation of blood in the splenic pulp.

**Hodgkin's Disease.**—The spleen is constantly enlarged in Hodgkin's disease, but as it is a disease of the entire reticulo-endothelial system, involving liver, lymph nodes, bone-marrow, etc., it is more conveniently considered in connection with disorders of that system.

**Leukemia.**—The spleen is involved in both forms of leukemia, but the lesions will be considered in connection with diseases of the blood. Infarcts are not uncommon.

**MYELOID METAPLASIA.**—A rare cause of splenomegaly is the development of abundant active marrow tissue in the organ. Large multinucleated cells of megakaryocyte type form a prominent feature (Fig. 427). Similar changes but less marked in degree may be present in the liver and lymph nodes. Immature red and white cells are seen in the circulating blood. The condition may be secondary to fibrosis of the bone marrow or osteosclerosis, but in other cases the marrow is normal. The name *agnogenic* (idiopathic) *myeloid metaplasia* has been applied to the latter group (Jackson *et al.*). It would appear that in such cases the reticulo-endothelial cells of the spleen have responded to a leukemic-like stimulus to a greater degree than those of the marrow, so that the condition may be regarded as a variety of aleukemic myelosis. In some cases a leukemic blood picture may develop. Jaundice may complicate the picture. If this is mistaken for a true hemolytic jaundice and the spleen is removed or radiated the result may be fatal, because the chief source of the patient's blood cells may be the myeloid tissue in the spleen.

**General Review of Splenic Enlargements.**—Enlargement of the spleen may be due to very different causes. The spleen is a contractile sponge, which may rapidly undergo marked variation in size. (1) In acute splenic swellings there is a great accumulation of inflammatory cells in the pulp, to which is probably added proliferation of the local endothelium. (2) The splenomegaly of hemolytic jaundice is characterized by an enormous accumulation of red blood cells in the splenic pulp, but the condition must be regarded as a reticulo-endothelial rather than a vascular disorder. (3) In polycythemia vera the spleen is moderately enlarged and firm owing to an accumulation of the excess red cells in the splenic reservoir. There may be cystic spaces filled with blood. (4) Splenic anemia appears to be due to vascular disturbances in the spleen caused by back-pressure in the portal and splenic veins. (5) The splenic enlargement of portal cirrhosis and the much lesser enlargement in chronic valvular disease of the heart is due to a similar cause. The increase in the fibrous reticulum which occurs in these conditions may be responsible for some of the enlargement. (6) The enlargement of amyloid disease is due to the great swelling of the individual connective-tissue fibers. (7) In the lymphoblastoma group (Hodgkin's disease, lymphosarcoma and leukemia), there may be hyperplasia both of the lymphoid and the reticulo-endothelial structures in the spleen. (8) The lipid storage diseases (Gaucher's disease, Niemann-Pick's disease, and hypercholesterolemic splenomegaly) form a group in which distention of the reticulo-endothelial cells with lipid is attended by great enlargement of the spleen. (9) The splenomegaly of kala-azar and possibly of malaria is due to a reticulo-endothelial proliferation. (10) The moderate enlargement in pernicious anemia may be due to myeloid transformation of the pulp.

## OTHER LESIONS OF THE SPLEEN

**TUMORS.**—Tumors of the spleen are curiously rare. Many primary tumors have been described, but the only ones which deserve mention are hemangioma and

lymphangioma. As the spleen plays the part of a filter it might be expected that secondary carcinoma would be very common. On the contrary it is comparatively rare. Almost every organ may be the seat of secondary growths, yet the spleen may remain free. This is in striking contrast to other reticuloendothelial organs such as the lymph nodes and bone-marrow. Tumor cells are undoubtedly arrested, but they are evidently unable to grow and multiply, so that they die out. The usual site of the primary tumor is the breast, the next most common being the lung.

**CYSTS.**—Cysts of the spleen are rare. Primary cysts of unknown origin may occur. Echinococcus cysts are less uncommon in countries where the disease prevails. Hemangioma and lymphangioma may cause cystic formation.

**ATROPHY.**—The spleen becomes markedly atrophic in old age, and may be only one-third of the normal weight. Similar atrophy may occur in wasting diseases of long duration. The capsule is thickened and wrinkled, and the cut surface has a markedly fibrosed appearance. The lymphoid tissue disappears, and the pulp is atrophic.

**PERISPLENITIS.**—Perisplenitis is a rather indefinite term which denotes fibrous thickening of the capsule, sometimes extreme in degree. It is seen in senile atrophy, and in some enlarged spleens the surface is covered with thick fibrous patches. The most extreme thickening is seen in Pick's disease.

**ACCESSORY SPLEENS.**—Accessory spleens or spleniculi are common. Usually there is only one, sometimes two, but in rare cases several hundred have been present. This is a reversion to the primitive condition in which the splenic tissue is not collected into a definite organ, but is strewn throughout the subserous coat of the gastro-intestinal tract.

## THE LYMPH NODES

The lymph nodes are definite glandular collections of lymphoid tissue, but this tissue is also scattered widely throughout the body in the alimentary canal, liver, spleen, thyroid gland, etc. It follows that general disease of lymphoid tissue will not be confined to the lymph nodes. The nodes do not consist only of lymphoid tissue. They contain reticulo-endothelial cells, and it is by virtue of these cells that the nodes play the part of filters and tend to retain any irritants which may reach them in the lymph stream. The pathology of the lymph nodes is often peculiarly difficult, because they possess a remarkable power of reacting to an irritant by proliferation and hyperplasia of their cells, so that it may be almost impossible to tell if we are dealing with an inflammatory condition or a true neoplasm. It is therefore of the greatest importance that when a practitioner sends an excised lymph node to the pathologist for diagnosis, he should at the same time send all the clinical information available. Too often the specimen is sent in without a word of history. It may be noted that the inguinal nodes are the least suitable for biopsy (although often chosen for the sake of convenience), because they frequently show evidence of previous infection (from legs and genitalia) in the shape of fibrosis and distortion. The site from which the gland was taken must therefore be stated.

Lymph nodes, like the spleen and thyroid gland, respond to disease by enlargement. There are therefore many causes of lymph node enlargement, but the more important of these may be divided into four main groups: (1) inflammation, (2) chronic granulomas, (3) lymphoblastomas or malignant lymphomas, and (4) secondary tumors.

## INFLAMMATION OF THE LYMPH NODES

**Acute Lymphadenitis.**—This is the result of virulent bacteria (staphylococcus, streptococcus) being arrested in the lymph node. The node is enlarged, painful, and tender, the cut surface varies from pink to gray, and a milky juice can be scraped from the surface. The *microscopic picture* varies with the severity of the inflammation. If this is extreme, the sinuses will be crowded with polymorphonuclear leucocytes, and patches of

necrosis will be scattered through the gland which eventually is converted into an abscess. It is comparatively seldom that the inflammation proceeds to suppuration. Usually the lesion clears up by resolution, and in such cases there is no necrosis, but merely marked hyperplasia of lymphoid and reticulo-endothelial tissue to which the enlargement of the gland is due.

It is the regional lymph nodes which drain an area of acute inflammation that develop acute adenitis. Some of the more important examples are the following: occipital and superficial cervical glands infected from pediculosis and wounds of scalp and ear, deep cervical glands from teeth and mouth, lateral pharyngeal glands from the pharynx with suppuration and the formation of a retropharyngeal abscess, axillary glands from the hands, inguinal glands from the genitals, leg, or foot. In all of



FIG. 428.—Chronic lymphadenitis.  
× 150.

these instances there may be a chronic lymphadenitis if the infection is less acute in type.

**Chronic Lymphadenitis.**—Chronic enlargement of a lymph node occurs when the node drains a focus of chronic inflammation. The gland is moderately enlarged, firm and homogenous. *Microscopically* the change is a proliferative rather than an exudative one. There is hyperplasia of the reticulo-endothelial cells, large numbers of the endothelial cells becoming swollen, rounded and cast off into the greatly dilated lymph sinuses, an appearance to which the name of *sinus catarrh* is given (Fig. 428). It may be noted in passing that lymphoid structures and hematopoietic structures in general respond to irritation by hyperplasia, so that it may be very difficult to distinguish between inflammatory and neoplastic conditions. This is a matter of supreme importance in connection with the

lymphoblastoma group. Chronic lymphadenitis is a very common condition. The cervical group is most often involved, due to infection from the mouth, tonsils, and teeth. Infection of the leg or the male genitalia will cause enlargement of the inguinal glands; infection in the lung, lesions in the bronchial glands, etc.

**MESENTERIC LYMPHADENITIS.**—In children and young adolescents there sometimes occurs an acute abdominal condition simulating appendicitis, diverticulitis, renal colic, etc., but in which the major finding at operation is inflammatory enlargement of the mesenteric lymph nodes in the ileocecal angle. In only a few cases can bacteria be demonstrated, and these are usually streptococci. Some of the cases are tuberculous. It is difficult to explain how the lesion in the lymph nodes gives rise to the clinical picture. Some of the symptoms may be due to spasm of the bowel.

**LIPOMELANOTIC RETICULAR HYPERPLASIA.**—Chronic dermatitis associated with pruritus may cause a characteristic type of hyperplasia of lymph nodes (Laipply). The hyperplasia may be extensive enough to be mistaken for lymphoblastoma. It is the reticular cells of the pulp which undergo hyperplasia. They frequently contain lipid vacuoles, and melanin pigment is found in large mononuclear cells. The fat and melanin are released from the skin by scratching and carried to the nodes, which they color yellow (fat) or brown (melanin).

## CHRONIC GRANULOMAS OF THE LYMPH NODES

**Tuberculosis.**—Tuberculosis is one of the common causes of enlargement of lymph nodes. The three groups most commonly involved are the cervical, bronchial, and mesenteric. The first is infected from the mouth and throat, usually the tonsils, the second from the lung, the third from the bowel. Mesenteric lymph node tuberculosis is likely to be caused by drinking tuberculous milk or swallowing tuberculous sputum. Although theoretically it is possible for the bacilli to pass through the intact wall of the bowel, in practice the more careful the examination the more often will an intestinal lesion be found. When the ileocecal group is involved in children there may be symptoms like those of acute appendicitis, *i.e.*, sudden onset of abdominal pain and rigidity, fever, vomiting, and a moderate leucocytosis. These symptoms are apparently due to spasm of the bowel.

The glands are at first discrete and firm, but when periadenitis occurs they become matted together. The cut surface shows tuberculous areas which are at first gray and translucent, but later become yellow, opaque, and caseous (Fig. 429). The entire gland may eventually become caseous and break down, so that a mere shell is left. In this way a cold abscess is formed which discharges on the surface (best seen in the neck), with the establishment of persistent sinuses which finally heal with deep scar formation. It must not be thought that this steady progression is the usual course. As a rule in response to appropriate treatment the condition clears up and does not go on to extensive caseation.

The *microscopic picture* shows the usual tuberculous follicles composed largely of epithelioid cells with a few giant cells (Fig. 430). In the caseous cases much of the structure of the node has disappeared. There is no tissue in which it is so hard to find tubercle bacilli; when present they are never numerous; it seems as if they are destroyed in the gland in some way.

As healing occurs fibroblasts proliferate and dense collagen fibers are laid down. Calcification is common in the caseous glands, particularly in the bronchial lymph nodes. However quiet the lesion may appear to be, there is always a danger that it may set up another focus elsewhere (bone, adrenal, etc.), by way of the blood stream. Sometimes the lesions are not discrete tubercles, but take the form of a *diffuse hyperplastic tuberculosis*, characterized by reticulo-endothelial hyperplasia and sheets of epithelioid

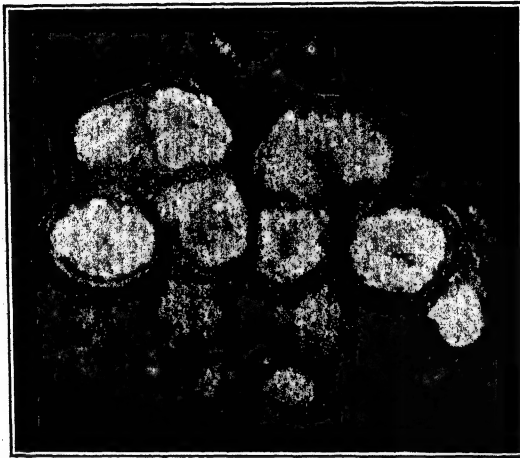


FIG. 429.—Tuberculosis of a lymph node showing several large caseous areas in the enlarged node.

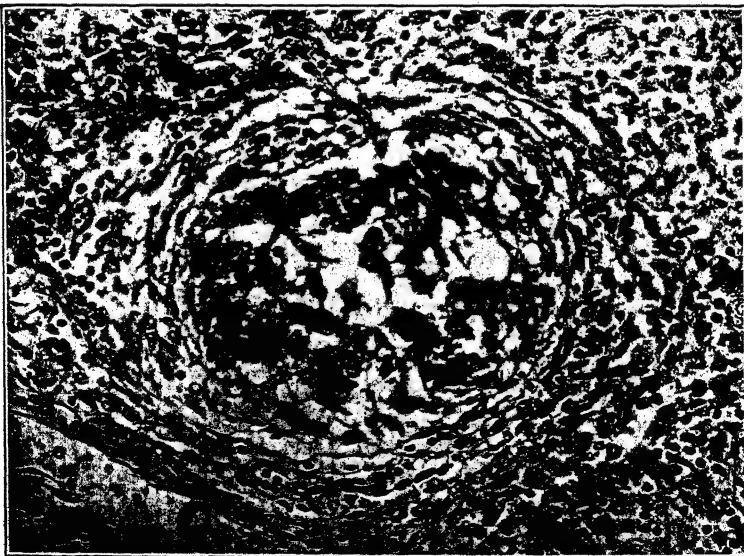


FIG. 430.—A tubercle. Epithelioid cells form the principal part of the tubercle.  $\times 250$ .

cells, but no caseation and no giant-cell formation. It is more than probable in the light of recent knowledge that many, perhaps most of these cases are really examples of sarcoidosis.

**Sarcoidosis.**—Although lesions of lymph nodes are prominent in this disease, many other organs are involved. It is, therefore, considered in relation to General Pathology on page 145.

**SYPHILIS.**—In a discussion of the differential diagnosis of lymph node enlargement syphilis is often mentioned. It is important to have a clear idea of what is meant when we speak of syphilis of the lymph nodes. The enlargement may occur in the primary, secondary, or tertiary stage. In *primary* syphilis the regional lymph nodes are enlarged and hard. In the usual type of lesion the inguinal glands are involved, but if the chancre is on the lip the submental nodes are enlarged. In the *secondary stage* the glands all over the body are moderately enlarged. In *tertiary* syphilis gummatous formation has been reported but is extremely rare. This is the point to remember in the differential diagnosis, even when the Wassermann reaction is strongly positive. The histology is not characteristic, *i.e.*, a proliferation of epithelioid cells, lymphocytes, and plasma cells. In the primary and secondary forms the demonstration of the *Spirochæta pallida* is usually easy.

## LYMPHOBLASTOMAS OR MALIGNANT LYMPHOMAS

**Hodgkin's Disease.**—This is a disease of the hemopoietic organs, *i.e.*, bone-marrow, lymph nodes, spleen, and liver. It is invariably fatal. Whether it is inflammatory or neoplastic in character is a matter of dispute. While studying the features of the disease the reader may weigh in his mind whether they point to an inflammatory or a neoplastic process.

**SYMPTOMS.**—The disease may occur at any age, but is commonest in middle life, usually in men. It is always fatal, but the duration varies greatly. The average case lasts between one and two years, but a very acute form may prove fatal in a few months, while chronic cases may last for years. I know of one case where a patient applied for life insurance sixteen years after a diagnosis of Hodgkin's disease had been made by biopsy independently in two first class laboratories of surgical pathology. In adults Hodgkin's disease is about twice as common as lymphosarcoma, but in children the incidence of the two diseases is about equal. The disease is usually first detected by an enlargement of the cervical glands, first on one side and then on the other, but deep glands (mediastinal, mesenteric) may have been enlarged long before the superficial ones become palpable. The spleen is enlarged to a considerable degree in 75 per cent of cases. The liver shows a slighter degree of enlargement in 50 per cent of the cases. A progressive anemia is constant, but the leucocytes show no uniform change. They may be increased or diminished in numbers, monocytes may be more numerous than normal, and occasionally there is a well-marked eosinophilia. Megakaryocytes have been found in the blood, and the blood platelets are often increased. Fever is common. Often this assumes the so-called Pel-Ebstein type, characterized by spells of mild fever lasting for a few days, and separated by intervals of a week or two of normal temperature. In other cases the fever is more continuous. Less common symptoms, but worthy of mention, are pruritus (itching), which may be present long before the glandular enlargement, pigmentation, and in rare instances infiltration of the skin. There may be dyspnea, cyanosis, paralysis, and other signs of pressure by the enlarged lymph nodes.



**LESIONS.**—The affected *lymph nodes* are enlarged, usually in groups. The greatest enlargement may be in the mediastinal, mesenteric, and retroperitoneal groups. The groups are not continuous with one another, thus differing from the usual picture of lymphosarcoma. For long the nodes may remain discrete, but eventually they may become fused as in tuberculosis. Sometimes there may be invasion of the surrounding tissue; thus invasion of the lung may take place from the mediastinal glands. The cut surface is pale gray, homogeneous, translucent, and moist, and has been likened, not inaptly, to fish flesh. Later it may become yellow owing to necrosis. The *spleen* is large and firm, but it often has not the homogeneous appearance of the lymph nodes, for scattered through it are numerous opaque patches, gray or yellow, like pieces of suet (Fig. 431).

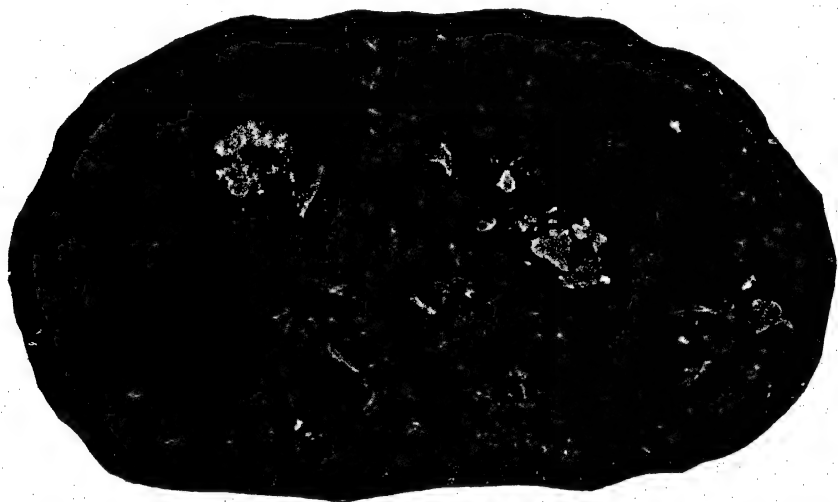


FIG. 431.—Enlarged spleen of Hodgkin's disease showing suet-like areas. (From Boyd's Surgical Pathology.)

These represent areas of "Hodgkin tissue," the change having commenced in the lymphoid follicles. Later the process becomes more diffuse. Small gray areas may be seen on the enlarged *liver*; these are lesions confined to the portal tracts. The *bone-marrow* may appear red and hyperplastic. Other organs may more rarely show lesions, *e.g.*, intestine, stomach, kidney, and wherever there happens to be lymphoid tissue. In exceptional cases the disease may be mainly or entirely confined to one organ, so that it is possible to have Hodgkin's disease of the lung, stomach, etc.

The *microscopic appearance* is the same wherever the lesions occur, but in any one site it may be extremely varied in character. Indeed its pleomorphism is its most characteristic feature. The lesion is mainly composed of large pale cells of "epithelioid" type. These large cells are probably derived from the reticulo-endothelial cells of the node. Even more characteristic is the appearance of very large or giant cells, some of which are mononuclear but many are multinucleated; when the nucleus is single

it may be convoluted or ring-shaped. These giant cells are the cells known as the Dorothy Reed or Sternberg cells (Fig. 432). The multinucleated forms frequently have two nuclei, one of which is the mirror-image of the other, the so-called "mirror-image giant cell." Lymphocytes, plasma cells, polymorphonuclear leucocytes and eosinophils may all be present. Eosinophils are particularly characteristic, and help to settle the diagnosis when it is in doubt, but it must not be thought that they are invariably present. Necrosis may appear later, but this is best seen in the spleen. There is a marked and characteristic increase of reticulum shown by silver staining. In the later stages there is dense fibrosis. In the earlier cellular

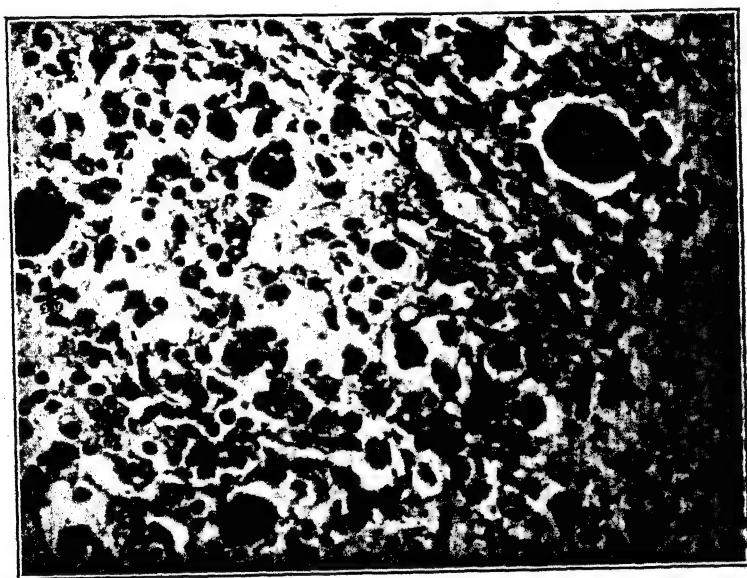


FIG. 432.—Hodgkin's disease. The cytological picture is characteristically pleomorphic. There are several large multinucleated cells of the Reed-Sternberg type.  $\times 350$ .

stage the lesion will respond for a time to radiation, but not in the late fibrotic stage. Sometimes there is not the pleomorphism of inflammation but rather the uniform cellular picture of neoplasia. The cells are large, of uniform size, with abundant cytoplasm and the large prominent nucleolus characteristic of malignancy. Mitoses are common. Reticulum formation is at a minimum. The lesion is much more invasive than is the ordinary form. Such cases have been called *Hodgkin's sarcoma*.

Jackson and Parker analyzed a large series of lymphadenopathies in which Reed-Sternberg cells are present and which may therefore be regarded as Hodgkin's disease. They find that the cases fall into 3 groups, which they call paragranuloma (38 cases), granuloma (237 cases) and sarcoma (51 cases). In the paragranuloma the disease is confined to the cervical lymph nodes although the spleen may also be involved, the capsule remains intact, the principal cell is the lymphocyte, and Reed-Sternberg cells are few and difficult to find; the lesion is easily mistaken for

lymphadenitis. The granuloma is the common phase of the disease. Its characteristics and those of the sarcomatous form have already been outlined.

**NATURE AND CAUSE.**—The cause of Hodgkin's disease is unknown and even the nature of the condition is uncertain. It has been regarded as: (1) an atypical form of tuberculosis; (2) a specific infective granuloma of unknown origin; (3) a tumor; (4) a transition form between a granuloma and a tumor.

(1) At various times during the past half century the view has been maintained that Hodgkin's disease is a special form of tuberculosis. Ewing, noting the not infrequent association of the two lesions in lymph nodes remarks that "tuberculosis follows Hodgkin's disease like a shadow." The arguments against this view seem more formidable than those in favor of it.

(2) A reasonable view appears to be that the disease is a specific infective granuloma of unknown origin, in which case the name Hodgkin's granuloma would be justified. The diversified cytological picture, the necrosis, and the subsequent fibrosis are all in favor of this idea. Against it may be set the invariably fatal outcome, and the regularity in the distribution of the lesions which is not seen in any of the other infective granulomata. It has been suggested that the infective agent is a filterable virus. Forbus and his associates have isolated *Brucella melitensis* from the lymph nodes, and by inoculating animals with the strains isolated they have produced granulomatous lesions of the lymphoid structures bearing some resemblance to those of Hodgkin's disease. They do not claim that *Brucella* is the cause of the disease. Lesions suggestive of Hodgkin's disease have been described in a number of domestic animals, particularly in swine by Forbus and Davis, but in no instance can these be regarded as identical with those of the disease as seen in man.

(3) The neoplastic theory is the most popular one at the present time. The chief points in its favor are the invariably fatal course and the resemblance to such an undoubtedly malignant condition as lymphosarcoma. The cytological picture is not that of cancer.

(4) The view that Hodgkin's disease occupies a position between the infective granulomata and tumors, as suggested by Symmers and others, offers an escape from an impasse. Without wishing too much to sit on the fence it may be said that the disease partakes of the characters of both of these conditions. The pleomorphism of the microscopic picture suggests an inflammatory lesion, whereas its local spread and its uniformly fatal termination are characteristic of malignancy.

**THE RELATION OF SYMPTOMS TO LESIONS.**—It is easy to correlate such symptoms as dyspnea and cyanosis with pressure of enlarged lymph glands in the neck or mediastinum. The glandular masses may press on the spinal nerves as they issue from the canal causing pain, paralysis, etc., or masses may be found lying within the spinal canal and pressing directly on the cord. The enlarged spleen will cause a sensation of abdominal fulness or heaviness. The anemia is due to involvement of the bone-marrow, and the variations in the blood picture (eosinophilia, etc.) may be attributed to the same cause. The cause of the fever is uncertain. The periodic or continuous fever may be connected with the necrosis which is so frequently present.

**HISTIOCYTIC MEDULLARY RETICULOSIS.**—In any series of cases of Hodgkin's disease there will be some which the pathologist is forced to call "atypical." It may well be that future observations may establish some of these cases as separate entities. Scott and Robb-Smith have distinguished one such group and named it histiocytic medullary reticulosis. The reticulososes form a group of diseases characterized by progressive cellular hyperplasia throughout the hemopoietic and lymphatic tissues, and in the example under consideration there is proliferation of histiocytes in the medulla of lymph nodes.

The lymph nodes show a generalized moderate enlargement, the spleen may be considerably or even greatly enlarged, the liver is slightly enlarged, and the marrow of the long bones red and hemorrhagic. Microscopically there is cellular proliferation in the medulla of the lymph nodes and spleen, the periportal tissue, and the bone-marrow. The medullary proliferation is composed principally of phagocytic histiocytes containing red blood cells and nuclear debris, and non-phagocytic prohistiocytes, large cells with irregular outline and dark nuclei, often showing mitotic figures; there may be giant prohistiocytes, but their dark and twisted nuclei are in sharp contrast to the pale "mirror-image" nucleus of the Dorothy Reed cell of Hodgkin's disease.

The principal clinical features are fever, wasting, generalized lymph node enlargement, together with enlargement of the liver and spleen, and in the final stages jaundice, purpura and anemia with profound leukopenia.

**Lymphosarcoma.**—Hodgkin's disease was first described a hundred years ago, but it was not until 1893 that Kundrat separated the condition known as lymphosarcoma from the general group of the lymphomas. The characteristic feature which serves to distinguish it from Hodgkin's disease is the fact that it arises in one group of lymph nodes or in one collection of lymphoid tissue and spreads to other groups of nodes apparently by way of the lymphatics. The spread tends to be continuous, whereas in Hodgkin's disease it is discontinuous. It may be easier for the clinician to make the distinction than for the pathologist who sees the end stage of widespread involvement in the autopsy room. In addition to the nodes there may be widespread involvement of the lymphoid tissue in the pharynx (tonsils, etc.), gastro-intestinal canal, spleen, bone-marrow, liver and other organs. Many of the other features of Hodgkin's disease may also be present. The spleen may be enlarged, although splenomegaly is not nearly so frequent as in Hodgkin's disease, fever is a common complication, and changes in the blood point to involvement of the bone-marrow. The most constant of these changes is a progressive secondary anemia, but there may be a relative or absolute lymphocytosis. Many cases are undoubtedly examples of aleukemic leukemia which have been unrecognized. It is often not realized by the physician that examination of a blood smear is more valuable than a biopsy. Pure classical lymphosarcoma of the type described by Kundrat is probably a rare disease.

The *gross appearance* of the lesions is very similar to that of Hodgkin's disease, but in lymphosarcoma there is a greater tendency to rupture of the capsule of the glands with invasion and destruction of the surrounding tissues. On the other hand, there is much less necrosis within the tumor, so that the yellow patches are not seen. The lymphoid tissue of the bowel may be much swollen so as to form nodular masses on the inner surface. The abdominal and thoracic cavities may be filled with tumor masses of

remarkable size considering the state of the superficial nodes (Fig. 433) and there may be extensive infiltration of the lungs.

The *microscopic appearance* shows complete replacement of the mature lymphocytes by much larger hyperchromatic cells with a small amount of basophilic cytoplasm and a round or oval nucleus with a fairly prominent nucleolus; mitoses may be present, but are not easy to recognize. The uniformity of cell type is an outstanding feature in comparison with the multiplicity of cell forms seen in Hodgkin's disease (Fig. 434). There is no increase in reticulum as shown by silver stains. Those reticulum fibers

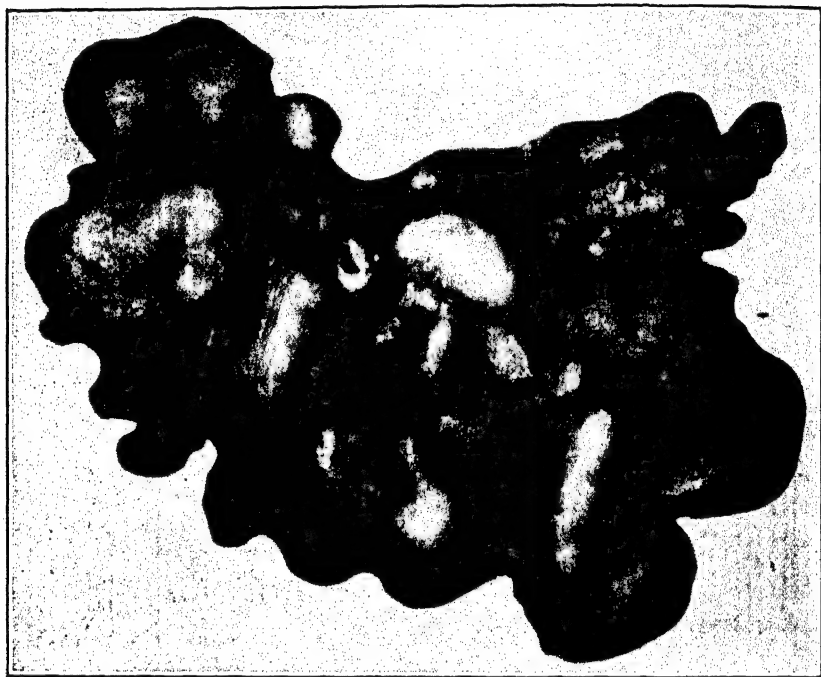


FIG. 433.—Lymphosarcoma. Mass of enlarged abdominal lymph nodes.

which are present represent the original content of the node, and these are dispersed by the infiltration of neoplastic cells, so that in a given field they appear to be decreased in number (Fig. 435).

In some cases there is a generalized lymph node enlargement rather than a neoplasia commencing in one region and gradually extending and becoming disseminated. In these cases the normal architecture is replaced by mature lymphocytes, and the picture is indistinguishable from that of lymphatic leukemia; only a blood examination can differentiate the two lesions. Such a condition may be called *lymphocytoma*; it may terminate as a lymphatic leukemia.

**Reticulum-cell Sarcoma.**—This tumor is commonly regarded as a form of lymphosarcoma under the name reticulum-cell lymphosarcoma. This

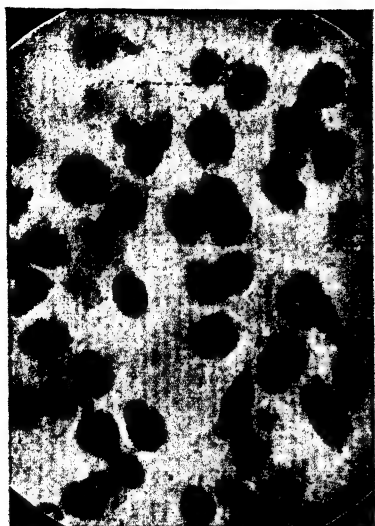


FIG. 434.—Lymphosarcoma. There is great uniformity of cell type.  $\times 650$ .



FIG. 435.—Lymphosarcoma; reticulum stain.  $\times 510$ .



FIG. 436.—Reticulum-cell sarcoma. Compare the size and form of the cells with those in Figure 434.  $\times 650$ .

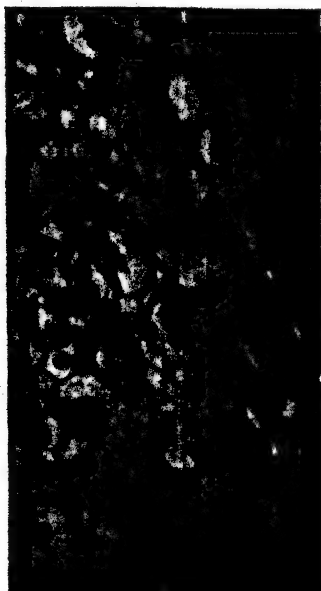


FIG. 437.—Reticulum-cell sarcoma; reticulum stain.  $\times 510$ .

is permissible in regard to tumors of lymph nodes, where the tumor arises from the reticular cells of the node. It may occur, however, in many other situations, including bone, where it forms one variety of bone sarcoma, so that it is better to speak of it as reticulum-cell sarcoma. It is a highly malignant disease, the average duration being less than two years. Although behaving like lymphsarcoma, it may occasionally occur as an isolated lesion, radical removal of which may result in apparent cure. Reticulum-cell sarcoma is a much commoner lesion of lymph nodes than pure lymphosarcoma.

The *microscopic appearance* is characteristic, but this is only true if the material is properly fixed, so as to prevent distortion by shrinkage, and suitably stained. The cytoplasm of the reticulum cell is usually abundant and faintly acidophilic (Fig. 436). The nucleus is double the size of that of a lymphocyte, and is commonly infolded, giving it a reniform appearance. Highly characteristic in well-fixed material is the presence of pseudopod-like processes of both cytoplasm and nucleus, indicating amoeboid activity in the living cell. The tumor cells may often be seen infiltrating the vein walls and almost closing the lumen. The pathognomonic feature is the distribution of reticulum the fibers show an intimate relationship to the tumor cells, encircling groups of cells and sending fibrils between and around individual cells (Fig. 437).

**INTERRELATIONSHIP.**—Although in typical cases there appears to be a sharp line of distinction between Hodgkin's disease, lymphosarcoma and reticulum-cell sarcoma, one of these conditions may blend with another. Thus biopsy may show one type, but subsequent autopsy may show another or more than one. Herbut and his associates believe that there are two chemical substances, one of which stimulates proliferation of the myeloid cells and the other the lymphoid cells. In Hodgkin's disease they occur in the urine in nearly equal proportions. The three diseases may arise from a common stem-cell, the reticulum cell.

**GIANT-FOLLICLE LYMPHOMA.**—There is a small group of cases which deserve to be separated from the general group of lymphosarcoma. The lesions may remain localized for a considerable time, and the disease is characterized by its prolonged duration of many years and by the marked sensitivity of the lesions to radiation. It has a tendency, however, to terminate as lymphosarcoma or reticulum-cell sarcoma. Both spleen and lymph nodes are involved, and the microscopic picture is one of extreme hyperplasia of the lymphoblastic cells of the germinal centers of the lymph follicles, so that the condition has been called follicular lymphoblastoma (Baehr and Klemperer). It is also known as Brill's disease, but this term is already used for a variety of typhus fever.

**BENIGN LYMPHOMA.**—This is an innocent tumor of a lymph node or group of nodes. It is very uncommon, and it is never safe to make the diagnosis from the microscopic picture alone, since this may be identical with that of lymphosarcoma. Indeed in all of these conditions the pathologist should be supplied with all the information possible before making a diagnosis. But if an enlarged gland or cluster of glands in the neck or groin increases slowly in size or remains stationary for a number of years without evidence of involvement of the rest of the lymphatic system, and if this gland when removed shows a replacement of the normal struc-

ture by a diffuse arrangement of small round cells such as is seen in lymphosarcoma, the blood meanwhile remaining normal, then it seems justifiable to make a diagnosis of benign lymphoma.

**Leukemia.**—The morbid anatomy of leukemia as well as the blood changes are considered in Chapter 30, but it is convenient to mention the condition of the lymph nodes in this place. In the lymphatic form of leukemia there is a general enlargement of the lymph nodes. Sometimes this is almost confined to the deep nodes in the thorax and abdomen so that the superficial glands may show little change. The *microscopic picture* is the same as that of lymphosarcoma, for the nodes are so crowded with lymphocytes that all normal structure disappears. Lymph node

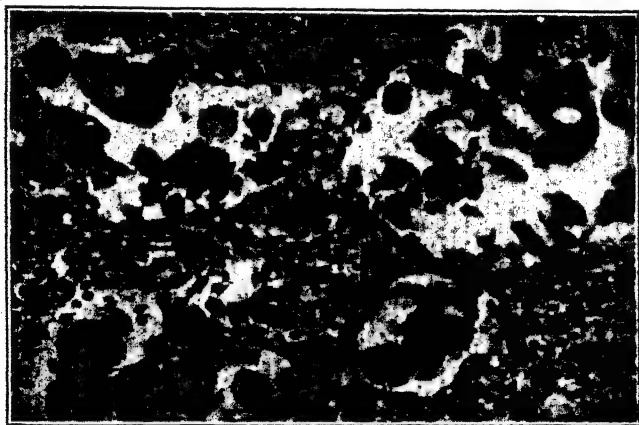


FIG. 438.—Secondary carcinoma of a lymph node. The lymph sinuses are distended by carcinoma cells.

enlargement does not form an essential part of the myelogenous form of leukemia, but it may occur, owing to the newly-formed primitive leucocytes (myelocytes) being detained in the sinuses of the nodes or possibly to a local formation by a process of myeloid metaplasia.

**INFECTIOUS MONONUCLEOSIS.**—This essentially benign condition, known also as glandular fever, bears some superficial resemblance to the group of diseases which has just been discussed. It is characterized by a mild degree of fever in young persons lasting for two or three weeks, a very sore throat, slight enlargement of the cervical lymph nodes and sometimes the axillary and inguinal groups, moderate enlargement of the spleen, and an increase in the mononuclear cells of the blood. The spleen is moderately enlarged in about 50 per cent of cases. The disease is never fatal, unless spontaneous rupture of the spleen occurs, a remarkable complication which has been reported not infrequently. Necrotic lesions are found in the liver not unlike those of infectious hepatitis, suggesting the possibility of a virus infection and explaining the mild jaundice which sometimes occurs. In addition, many of the organs may show leukemic-like infiltration by mononuclear cells similar to those which dominate the blood picture. The total leucocyte count rarely exceeds 20,000, but the percentage of mononuclears may be from 50 to 95 per cent of the total count, so that at first a distinction from lymphatic leukemia may be



impossible. The increase may be in small lymphocytes or in large mononuclears, and it is possible that these may be monocytes rather than lymphocytes. The lymph nodes show lymphoid hyperplasia, but traces of the normal architecture still remain. The condition is apparently due to bacterial infection through the tonsils or the upper respiratory tract, as a result of which lymphoid tissue is unduly stimulated, many of the newly-formed cells appearing in the blood stream. The blood contains heterophile antibodies, *i.e.*, the serum will clump sheep's red cells even in high dilution (Paul-Bunnell test). This is a useful test in doubtful cases, but it is by no means specific, for it may be negative in infectious mononucleosis and positive in virus pneumonia.

**Secondary Tumors.**—A carcinoma tends to metastasize to the regional lymph nodes. The cancer cells are first found in the peripheral lymph sinus and then in the medullary sinuses (Fig. 438). As the tumor cells grow they destroy the lymphoid tissue, until finally the entire node is a mass of carcinoma. The secondary growth may be more or less differentiated than the primary tumor. When the tumor cells break through the capsule the gland becomes firmly adherent to the surrounding tissues, being then inoperable. Malignant melanomas, also metastasize to the lymph nodes, but sarcomas rarely do, spreading as a rule by the blood stream.

## THE THYMUS GLAND

The thymus is partly epithelial and partly lymphoid in structure. At first it is entirely epithelial, being derived from the third branchial cleft, but later in embryonic life it becomes invaded with lymphocytes. The epithelium persists as the Hassall's corpuscles and the cells of the reticulum. The cytoteticulum is derived from the endodermal third branchial pouch, the Hassall corpuscles from the ectodermal cervical sinus.

The size of the thymus is its most important feature. No idea of the size during life can be obtained unless the patient has died suddenly, for the gland undergoes a rapid and remarkable shrinking as the result of infection, starvation, and other hostile influences; this shrinkage takes place at the expense of the lymphocytes. In emaciated children the gland may weigh only 2 or 3 grams instead of the normal 15 or 20 grams. It follows that in cases of sudden death, whether in the child or adult, the thymus may appear to be abnormally large. The average weight at birth is 13 grams, and this gradually increases until at puberty it weighs 35 grams or more. After that period there is a gradual atrophy. The fall in weight after puberty suggests that the thymus exerts some influence on genital development.

*Hyperplasia* of the thymus is a constant feature of Graves' disease, where it forms part of a general thymic-lymphatic hyperplasia. There is said to be hyperplasia in Addison's disease, acromegaly, castration, myasthenia gravis, and after thyroid feeding.

## STATUS THYMICO-LYMPHATICUS

In cases of sudden death from no obvious cause the thymus and the lymphoid tissue throughout the body may be found to be enlarged, and it is the custom to attribute death in these cases, especially when there is a coroner's inquest, to "status lymphaticus" or "enlarged thymus." There is a remarkable difference of opinion at the present day regarding the im-

portance and even the existence of status lymphaticus. Marine, Warthin, and others describe the condition as a constitutional defect associated with lowered resistance and characterized by hyperplasia of the thymus, lymph nodes and lymphoid tissue in general, together with underdevelopment of the adrenals, gonads, and cardiovascular system. Greenwood and Woods, on the other hand, after a most careful statistical investigation describe status thymico-lymphaticus as a good example of the growth of medical mythology, in which a nucleus of truth is buried beneath a pile of intellectual rubbish, conjecture, bad observations, and rash generalization, and that it is as accurate to attribute the cause of death to "an act of God" as to status lymphaticus.

The writer has not had sufficient experience with cases of sudden death to enable him to express an opinion on this difficult matter. Two facts, however, must be admitted. The first is that certain persons have an abnormally low resistance to drugs, anesthetics, vaccines, serums, and such poisons as arsphenamine and cocaine. In such persons death may follow the most trivial of causes, such as extraction of a tooth, tonsillectomy, a slight blow, or taking a cold bath. The second fact is that in some persons there is a remarkable lymphoid hyperplasia affecting the lymphoid tissue of the throat, nasopharynx, intestinal canal, lymph nodes, and frequently the thymus, associated with hypoplasia of the adrenals, heart, and great vessels. It has been shown experimentally that removal of the adrenals lowers the resistance of rats to morphine as much as 400 times. Modern knowledge regarding the relationship of the adrenal cortex to resistance to stress and lymphoid tissue development suggests that it is the small adrenal rather than the large thymus which is the source of danger. I may quote the following case from the medico-legal practice of my colleague Dr. Erb, which is surely sufficient proof that the concept of death from status lymphaticus is not a pure myth. One of a group of children who were playing on the road was struck down by a motor car and injured. He did not die, but a little lad watching the accident from an adjoining lawn fell dead. At postmortem the child was found to have an enlarged thymus, a thin-walled hypoplastic aorta, and marked hyperplasia of the lymphoid tissue throughout the body. The cause of death in these cases is quite obscure. The immediate cause is stoppage of the heart, which may be attributed to vagal stimulation. Pressure of a much enlarged thymus on the trachea in children has been known to produce dyspnea, but such pressure has nothing to do with the actual death. There seems to be no justification for the term thymic death, for there is no proof that the thymus has anything to do with the stoppage of the heart.

**Sudden Death.**—A brief note may be allowed here on the subject of sudden death, *i.e.*, death occurring unexpectedly in the course of a few minutes. When called upon to perform an autopsy on such a case it is well to bear seven possibilities in mind: (1) cardiac, (2) pulmonary, (3) abdominal hemorrhage, (4) cerebral hemorrhage, (5) traumatic shock, (6) poisons, and (7) status lymphaticus. Sudden *cardiac* death is discussed elsewhere. It includes coronary thrombosis, coronary occlusion by atheroma causing sudden myocardial failure, syphilitic aortitis, and rupture of the heart or of an aortic aneurism. Sudden *pulmonary* death

may be caused by pulmonary embolism, edema of the glottis, laryngeal diphtheria, and foreign bodies in the pharynx and larynx. Spasm of the glottis is a frequent cause of asphyxia in drowning. In children inhalation of stomach contents may cause fatal spasm of the glottis. The rare cases of death from anaphylaxis may be placed in this group. Fatal *abdominal hemorrhage* may occur into the stomach from a gastric ulcer or a varicose vein at the lower end of the esophagus, or into the adrenals especially in children. In the latter case death is due to acute adrenal insufficiency rather than to loss of blood. Ruptured tubal pregnancy and ruptured abdominal aneurism may be included here. *Cerebral hemorrhage* may be rapidly fatal if massive enough (into the ventricles or a cerebral tumor) or if into a vital center (medulla). Sudden death may occasionally follow epileptiform seizures. *Traumatic shock* may cause death at once or after a few minutes; the heart stops beating. *Poisons* must be borne in mind if no cause of death can be found. The odor of the gastric contents may indicate acute alcoholism or prussic acid (smell of bitter almonds). The contents of the stomach should be placed in a jar and sealed. *Status lymphaticus* has already been considered. Of these varied causes by far the commonest are trauma and cardiac failure. It is they which are likely to result in really sudden death. The others (hemorrhage, etc.) are more apt to bring about death in the course of some hours. In one group of cases of *instantaneous* death, *i. e.*, death in a matter of seconds, not minutes or hours, no lesions may be found in vital organs other than those which in other persons are compatible with good functional capacity. Such cases are probably examples of fatal syncope due to increased irritability of nerve endings and hyperactivity of the reflexes, a physiological state which may be caused by transient undetectable factors (chemical, emotional, etc.) as well as by organic lesions (Weiss). Most of these cases may be put down to vagal inhibition with sudden cessation of the heart's action.

## TUMORS OF THE THYMUS GLAND

The only tumor which need be mentioned is the *malignant thymoma*. This constitutes one variety of mediastinal tumor and is commonly taken for a lymphosarcoma. It is highly malignant, compresses the trachea and other structures, invades the lungs, and metastasizes to bronchial, cervical and axillary glands, and sometimes to distant organs. The structure varies, and this is natural, because the thymus arises from two cell systems, the one lymphoid and the other epithelial. The usual type of picture is lymphosarcomatous, but occasionally it is frankly carcinomatous. It seems probable that these two types arise from one or other of the two cell systems. Tumors of the thymus are occasionally present in myasthenia gravis. This has suggested the removal of the thymus, whether or not a tumor is present, in the treatment of this condition, a procedure which has met with marked success.

## ADDITIONAL READING

- Acute Splenic Swelling.** RICH, *et. al.*: Bull. Johns Hopkins Hosp., 1939, 65, 311.  
**Banti's Disease.** DÜRR: Ziegler's Beitr. z. path. Anat., 1924, 72, 418. RAVENNA: Arch. Int. Med., 1940, 66, 879.  
**Gaucher's Disease.** GRAHAM AND BLACKLOCK: Arch. Dis. Childhood, 1927, 2, 267.  
 OBERLING: Ann. d'anat. path., 1926, 3, 23. PICK: Med. Klin., 1924, 254, 782.

- Giant-follicle Lymphoma.** BAEHR, *et. al.*: Am. J. Path., 1931, 7, 558. BAGGENSTOSS AND HECK: Am. J. Med. Sci., 1940, 200, 17. BRILL, *et. al.*: J. A. M. A., 1925, 84, 668. SYMMERS: Arch. Path., 1942, 34, 385.
- Histiocytic Medullary Reticulosis.** SCOTT AND ROBB-SMITH: Lancet, 1939, 2, 194.
- Hodgkin's Disease.** FORBUS AND DAVIS: Am. J. Path., 1946, 22, 35. GORDON: In Rose Research on Lymphadenoma, Bristol, 1932. JACKSON AND PARKER: New England J. Med., 1944, 231, 35. POSTON AND PARSONS: J. Infect. Dis., 1940, 66, 86. WALL-HAUSER: Arch. Path., 1933, 16, 522.
- Hyalinosis in Sarcoid.** TEILUM: Am. J. Path., 1948, 24, 389.
- Hypersplenism.** DAMESHEK AND ESTREN: Med. Clin. N. America, 1950, 34, 1271. DOAN: Bull. New York Acad. Med., 1949, 25, 625. LEFFLER: Am. J. Path., 1952, 28, 303. VON HAAM AND AWNY: Am. J. Clin. Path., 1948, 18, 313.
- Infectious Mononucleosis.** BLAND: Brit. J. Exper. Path., 1931, 12, 311. CONWAY: Arch. Path., 1938, 25, 200. DARLEY, *et. al.*: Am. J. Med. Sci., 1944, 208, 381. ZIEGLER: Arch. Path., 1944, 37, 196.
- Letterer-Siwe's Disease.** FARBER: Am. J. Path., 1941, 17, 625. JAFFE AND LICHTENSTEIN: Arch. Path., 1944, 37, 99. SCHAFER: Am. J. Path., 1949, 25, 49.
- Lipoid Histiocytosis.** BLOOM: Am. J. Path., 1925, 1, 595. PICK: Am. J. Med. Sci., 1933, 185, 453 and 601. ROWLAND: Arch. Int. Med., 1928, 42, 611. THANNHAUSER: Lipidosis: Diseases of the Cellular Lipid Metabolism, New York, 1940.
- Lipomelanotic Reticular Hyperplasia.** LAIPPLY: Arch. Int. Med., 1948, 81, 19.
- Lipophosarcoma.** CALLENDER: Am. J. Path., 1934, 10, 443. CUTLER: Arch. Surg., 1935, 30, 405. ERLICH AND GERBER: Am. J. Cancer, 1935, 24, 1.
- Malignant Lymphoblastoma.** GALL AND MALLORY: Am. J. Path., 1942, 18, 381. HERBUT, *et. al.*: Am. J. Path., 1945, 21, 233.
- Mesenteric Lymphadenitis.** STRÖMBECK: Acta. chir. Scandinav. (Supp. 20), 1932, 70, 1. WILENSKY: Arch. Surg., 1941, 42, 71.
- Myeloid Metaplasia of Spleen.** HELLER, *et. al.*: Am. J. Path., 1947, 23, 327. JACKSON, *et. al.*: New England J. Med., 1940, 222, 985. LEVINSON AND LIMARZI: Am. J. Clin. Path., 1947, 17, 449.
- Primary Reticulo-endothelial Granulomas.** DENNIS AND ROSAHN: Am. J. Path., 1951, 27, 627.
- Reticulosis.** ROBB-SMITH: J. Path. and Bact., 1938, 47, 457.
- Reticulum-cell Sarcoma.** STOUT: J. A. M. A., 1942, 118, 968. SUGARBAKER AND CRAVER: J. A. M. A., 1940, 115, 17 and 112. WARREN AND PICENA: Am. J. Path., 1941, 17, 385.
- Schüller-Christian Syndrome.** HORSFALL, JR., AND SMITH: Quart. J. Med., 1935, 4, 37.
- Splenic Neutropenia.** WISEMAN AND DOAN: Ann. Int. Med., 1942, 16, 1097.
- Splenic Structure.** KNISELY: Anat. Rec., 1936, 65, 23 and 131. ROBINSON: Am. J. Path., 1926, 2, 341; 1928, 4, 309.
- Status Lymphaticus.** MARINE: Arch. Path., 1928, 5, 661. SYMMERS: Am. J. Surg., 1934, 26, 7. TAYLOR: Proc. Roy. Soc. Med., 1939, 33, 119.
- Sudden Death.** HAMMAN: Bull. Johns Hopkins Hosp., 1934, 55, 387. WEISS: New England J. Med., 1940, 223, 793.
- Thymoma.** FOOT: Am. J. Path., 1926, 2, 33. WILSON AND PRITCHARD: Canad. Med. Assn. J., 1945, 53, 444.

## THE BLOOD

## THE BONE-MARROW

THE cells of the blood in extra-uterine life are formed in the bone-marrow. It is only the red marrow which is blood-forming, the yellow marrow consisting of nothing but fat. In the adult the red marrow is confined to the flat bones, *i.e.*, vertebræ, sternum, ribs, skull, and pelvic bones. In the child, on the other hand, all the bones are filled with red marrow. About the seventh year microscopic evidence can be detected of a change from the red to the yellow marrow, the change being evident to the naked eye at the fourteenth year, and by the twenty-first year all the red marrow of the long bones has become replaced by fat and is therefore of the yellow type. The change first appears in the distal bones and is always most complete in them. A little red marrow is left in the proximal bones, and at the proximal end of these bones, *i. e.*, at the upper end of the femur and humerus. When functional hyperplasia of the marrow occurs, it first becomes apparent in the proximal bones and only later involves the distal bones. The marrow of the femur is often red when that of the tibia is still yellow. Red marrow is much more vascular than yellow marrow. It is natural, therefore, that secondary carcinoma should be more common in the humerus and femur than in the bones of the forearm or the tibia. Marrow occurs only in bone. This is true even for such heterotopic bone as may be formed in a tuberculous scar in the lung or in the media of an artery. The explanation of this constant association appears to lie in the fact that marrow can be observed to arise from the endosteum of bone in the experimental animal (Steinberg and Hufford). The technic employed was complete extirpation of the marrow of the tibia, with subsequent regeneration. The presence of fat spaces is a prerequisite to the formation of myeloid elements.

It is easy to describe the *cells* which may occur in red marrow, but it is not so easy to recognize them under the microscope. Far the most numerous cells are the myelocytes, followed by the normoblasts. There are three times as many white as red cells. Myeloblasts and megaloblasts are rarely seen in normal marrow. The myelocytes can be recognized by the granules in the cytoplasm. The normoblasts are smaller, and present a "drop of ink" appearance, the intensely dark nucleus having so little of the characteristic red cytoplasm around it that it may be impossible to detect the latter, so that the cell may be mistaken for a lymphocyte. It is safe to say that nearly all lymphoid-like cells in the marrow are normo-

blasts. In health multiplication takes place at the normoblastic level and megaloblasts are seldom seen.

The large megakaryocyte with its basket-work nucleus and the polymorphonuclear leucocytes are easily recognized. The best studies of marrow cells are made on smears of marrow obtained by sternal puncture during life. Within three hours after death the marrow presents a distorted picture, and even after one hour the cell staining is not as good as during life.

The bone-marrow readily undergoes *functional hyperplasia*, as a result of which a very extensive actively functioning tissue is formed. The chief evidence of hyperplastic activity is the conversion of the yellow marrow into the red variety. The bony trabeculae of the yellow marrow become absorbed, and if the hyperplasia is marked there may be absorption of the compact bone so that the medullary canal is widened. First the proximal and then the distal bones become filled with red marrow. If the marrow of the femur is examined routinely at autopsy the observer will be surprised to find how often it is red instead of yellow owing to the presence of terminal infections, etc. The two chief causes of functional hyperplasia are anemia and infection; in the first the response is mainly erythroblastic, in the second it is mainly leucoblastic, but pure forms of the reaction are seldom seen. In the leucoblastic reaction the new cells are mainly myelocytes. In the erythroblastic reaction they may be either normoblasts or megaloblasts. As already mentioned, it is easier to describe the types of reaction than to recognize the individual cells under the microscope.

**The Bone-marrow in Blood Diseases.**—Modern hematology has made its great advances on the basis of bone marrow aspiration. The marrow must be considered in every disease of the blood. It will usually show some change. This change may be primary as in pernicious anemia and leukemia, or it may be secondary as in secondary anemia. Instead of describing these changes here it will be more convenient to take them up when the individual diseases are considered.

## THE ANEMIAS

Anemia is a condition of the blood in which the concentration of hemoglobin is below normal. This may be brought about in two ways: there may be excessive loss of blood either from hemorrhage or hemolysis (hemorrhagic and hemolytic anemias); there may be deficient blood formation (deficiency anemias). (1) In anemia due to acute hemorrhage the cells and hemoglobin are reduced equally; it is a normocytic and normochromic anemia. In chronic hemorrhage the picture is that of an iron deficiency anemia with low color index (hypochromia). When anemia is due to hemolysis the blood bilirubin is raised and the number of reticulocytes is increased. (2) The normal growth of red cells requires nonspecific building stones and also certain specific principles. The *building stones* may not be manufactured properly because of the action of toxins, cachectic conditions, etc., on the marrow or because of primary deficiency and atrophy of the marrow. The *specific principles* are iron and the antianemic principle of the liver. Iron is necessary for normal maturation at the

normoblastic level and the filling of the red cells with hemoglobin. There may be too little iron in the food, it may be poorly absorbed, or it may be lost from the body (chronic hemorrhage). The result is a hypochromic microcytic anemia in which the cells are not much reduced in number but are small and have too little hemoglobin; the anemia responds to iron. The antianemic principle of the liver is necessary for the maturation of megaloblasts. It is formed in the stomach by the action of an intrinsic factor in the gastric secretion on an extrinsic factor in the diet. The gastric factor (intrinsic) may be lacking, the result being pernicious anemia; or the food factor (extrinsic) may be lacking, the result being the tropical nutritional anemias; or the antianemic principle may not be properly absorbed (due to intestinal disease) or stored in the liver (due to cirrhosis, etc.). In all these cases there is a macrocytic hyperchromic anemia, which responds well to liver.

From the above summary the causes of the anemias may be classified as follows: (A) *Increased blood loss*: (1) hemorrhage (2) hemolysis (B) *Decreased blood formation*: (1) Deficiency of specific substances: (a) iron, (b) antianemic principle or the factors which create it. (2) Depression of marrow function (aplasia): (a) nephritis, toxemias, cachexias; (b) idiopathic aplastic anemia. The various anemias will be considered under the headings of Deficiency, Hemolytic and Aplastic Anemias.

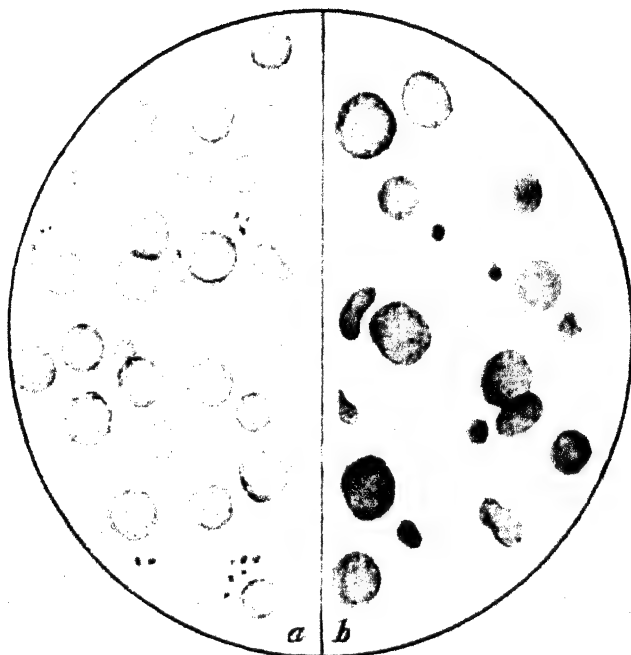
### THE DEFICIENCY ANEMIAS

Of late years it has become increasingly evident that a number of the anemias have a nutritional basis. These are the nutritional or deficiency anemias. The group comprises pernicious anemia, chlorosis and idiopathic hypochromic anemia, to which may be added the anemia of sprue, coeliac disease, and possibly other forms of anemia. Some element necessary for blood formation may be lacking in the diet, or the body may be unable to utilize it even though it is present.

**Pernicious Anemia.**—The form of anemia commonly called pernicious was first described by Addison, so that it is sometimes known as Addison's anemia, a more appropriate term than pernicious anemia, as the disease is no longer "pernicious" since the introduction of liver therapy. But old names in medicine are hard to displace.

**CLINICAL FEATURES.**—The disease is usually one of middle age, affecting the two sexes equally, although occurring at an earlier age in women. The symptoms are those of a gradually progressive anemia. As Addison remarked in his original contribution: "It makes its approach in so slow and insidious a manner that the patient can hardly fix a date of his earliest feeling of the languor which is shortly to become so extreme." The course is marked by very remarkable intermissions during which the symptoms clear up and the blood returns toward the normal. In exceptional cases the red cell count may rise from 1,000,000 to 3,000,000 in the course of two or three weeks without any treatment whatever. Before the introduction of liver therapy the course was progressive and uniformly ended fatally, but varied extremely in its degree of acuteness. Now that patients no longer die, they show a tendency to develop cancer of the stomach. The

## PLATE XXV



### *a.* Hypochromic Anemia

The cells are pale and none are larger than normal. Platelets are present.

### *b.* Hyperchromic Anemia

Film of pernicious anemia showing macrocytosis as well as poikilocytosis, anisocytosis and hyperchromia. There are no platelets.



symptoms are those of any severe anemia, *i. e.*, pallor, shortness of breath, palpitation, edema. But there are two features which are characteristic of the pernicious form of anemia; these are achlorhydria and spinal cord symptoms.

The *achlorhydria* is often spoken of as *achylia gastrica*. The two terms are not synonymous, for the latter indicates suppression of all the elements of the gastric juice—pepsin and rennin as well as hydrochloric acid. This suppression often occurs in pernicious anemia, but it is not so constant as achlorhydria. It is a complete achlorhydria, whereas that of carcinoma of the stomach is never constantly complete. It is probable that the achlorhydria antedates the development of the anemia by a considerable period. It is often associated with loss of appetite (anorexia), which may cause a wrong diagnosis of cancer of the stomach. *Spinal cord symptoms* appear in about 5 per cent of the cases, and take the form of ataxia, sensory disturbances, spasticity, and loss of vibration sense in the bones of the leg. The symptoms bear no relation to the severity of the blood changes nor even to their presence, for they may develop before the appearance of any alteration in the blood. In addition to spinal cord symptoms minor nervous symptoms are very common, occurring in about 80 per cent of the cases. They take the form of numbness, tingling, and paresthesias in the arms and legs. These common symptoms are not related to cord lesions, being due to a mild peripheral neuritis.

**BLOOD CHANGES.**—The blood picture varies greatly with the stage of the disease, being very abnormal during an exacerbation but often showing little change during an intermission. The changes described below are those of a severe relapse. All the formed elements of the blood are diminished in number, the red cells, the leucocytes, and the platelets. In severe cases the *red cells* may only number 1,000,000 or less. Any anemia in which the red cell count is below 2,000,000 is probably, but not necessarily, pernicious in type. In remissions the count may be as high as 4,000,000. The hemoglobin is also diminished but not in proportion, so that the *color index* (ratio of hemoglobin percentage to percentage of red cells) is high and may be above 1, even as high as 1.5. The red cells, at least many of them, are well colored; they are hyperchromic, in striking contrast to the condition in the hypochromic or achromic forms of anemia (Plate XXV, B). More important than the number of red cells is the presence of qualitative changes. Just as the characteristic lesion of pernicious anemia is a megaloblastic reaction in the bone-marrow, so the characteristic change in the blood is a megalocytic or macrocytic anemia. The large *macrocytes* can be seen readily in a stained film, but more important than the presence of occasional large cells is the fact that the *average* size of the red cells is above normal. The average diameter of normal red cells is 7.5 microns, while the average in pernicious anemia may be as high as 8.5 microns (Price-Jones). Pernicious anemia belongs to the megaloblastic and macrocytic group of anemias. The variation in size, which normally is from 6 to 9 microns, in pernicious anemia may be from 4 to 12 microns. Many of the red cells are therefore smaller than normal. These are called *microcytes*, and the variation is known as *anisocytosis*. The large cells are hyperchromic, but the microcytes are hypochromic. *Poikilocytosis* (*poilikos*,

manifold) may be marked, the cells varying greatly in shape, many being tailed or shaped like a cocked hat.

The tendency in pernicious anemia is for the red cells to revert to a more primitive or embryonic type, for the essence of the disease is a failure on the part of the red cells of the marrow to mature sufficiently quickly. The megaloblastic reaction of the marrow and the macrocytic type of anemia are evidence of this tendency. Many of the cells show *polychromatophilia*, the cytoplasm being of a slaty color owing to having taken up both the red and blue stain. This is most marked in the megaloblasts. The cytoplasm of the original red cell is entirely basophilic. It becomes partly

acidophilic as hemoglobin begins to appear, and at this stage shows polychromatophilia. It is only when the cell is mature that it becomes completely acidophilic. *Basophilic stippling* (granular degeneration) may be present; it is merely another manifestation of the same basophilic substance, which in this instance takes the form of fine granules staining blue. The presence of *reticulocytes* is an indication of immaturity, for the reticulum is another form of the same basophilic material. In health reticulated red cells form 1 per cent of the total count, but in pernicious anemia they usu-

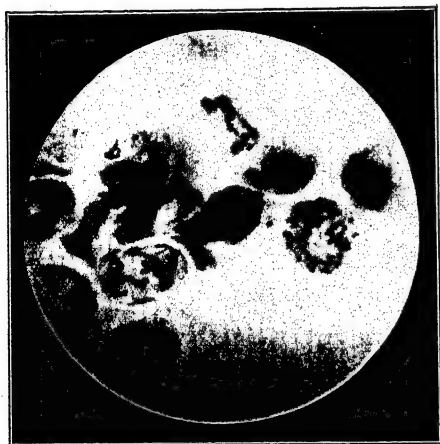


FIG. 439.—Increase of reticulocytes in pernicious anemia. Four of the red cells show reticulation.  $\times 1400$ .

ally form 5 per cent (Fig. 439). The best indication of successful activity on the part of the marrow is an increase in the reticulocyte count. There is a marked rise in a remission, and a specially great increase when liver therapy is commenced. In aplastic anemia, where the bone-marrow shows no activity, there is a complete absence of reticulocytes. The reticulation is not shown in an ordinary film; vital staining has to be used.

*Nucleated red cells* provide another indication of immaturity. They may be normoblasts or megaloblasts. The latter are commoner and much more characteristic, as normoblasts may occur in any severe anemia, but megaloblasts are seldom found except in pernicious anemia. The megaloblast is much larger than a normoblast, its nucleus is larger and more open, and the cytoplasm is polychromatophilic or even basophilic. The nucleus may show mitosis. They can always be found if the count is below 2,000,000, but when it is above 2,500,000 it may be difficult to find a single megaloblast. Owing to the immaturity of the red cells in pernicious anemia, their fragility is diminished rather than increased, for it is the older cells which become more fragile when tested with hypotonic salt solution.

A word may be devoted here to what is known in hematology as the "megaloblast problem." The term megaloblast has been used in two different senses. Ehrlich applied the word originally to an essentially abnormal cell which is only present in pernicious anemia, and this practice has been followed by European hematologists. Florence Sabin, on the other hand, in her studies on the development of the blood cells used the term to denote the earliest identifiable member of the maturing normal red cell series. It would appear that red cells can develop along two different but parallel routes, one normal and the other abnormal (pernicious anemia). It is possible to distinguish the Ehrlich megaloblast (abnormal) from the Sabin megaloblast (normal) in stained marrow films. The abnormal megaloblast is larger, has a finer reticular nuclear chromatin, and more or less hemoglobin content than the corresponding cell of the normal series. The end result is a macrocyte, whereas the end result of the normal series is an erythrocyte.

The *leucocytes* diminish in number, so that there is a *leucopenia*. This affects chiefly the polymorphonuclears, so that there is a relative lymphocytosis. The polymorphonuclears are much more lobed in pernicious than in other forms of anemia. This is a useful practical point. Indeed it has been said that in studying the anemias more may be learned from looking at the white cells than at the erythrocytes. There is no leucocytosis even in acute infections. The fault lies in the marrow. This is filled with myelocytes, but they fail to mature, so that there is a decrease in the polymorphonuclears. Myelocytes are not infrequently found in the blood. The *platelets* are much diminished in number (thrombocytopenia), and they may disappear altogether. The *plasma* shows a characteristic yellow tinge due to an increased bilirubin content, the result of increased blood destruction, and there is a positive indirect van den Bergh reaction, with an increase of urobilinogen in the urine. These serological findings are of great value in those difficult cases where the cytological picture is so indeterminate that no definite diagnosis can be made.

**MORBID ANATOMY.**—The lesions of pernicious anemia are partly primary in character, but mostly secondary either to the anemia or to increased blood destruction. The two most constant pathological findings are a megaloblastic type of bone-marrow and marked siderosis. The intensity of these lesions will depend on the stage of the disease at the time of death. If the patient dies during an acute exacerbation, the megaloblastic reaction, the siderosis, and all the secondary lesions will be marked, whereas they may be trivial if the patient dies of some intercurrent disease during a remission. This is not true of lesions of the spinal cord and possibly those of the alimentary tract. It will be seen from the following description that the lesions may be divided into five groups: (1) Those due to the anemia (fatty degeneration, hemorrhages); (2) bone-marrow changes; (3) siderosis, increased phagocytosis by the reticulo-endothelial cells, and other evidences of blood destruction; (4) lesions of the alimentary tract; (5) lesions of the nervous system.

The *skin* is of a lemon-yellow color, and has not the pure pallor of secondary anemia. There is a remarkable absence of wasting, and the abundant fat is also lemon-yellow. The *muscles* are normal or deep red in color.

Petechial *hemorrhages* are common in the serous membranes and can be seen during life in the retina. These changes are due to fatty degeneration of the walls of the small vessels. The fatty degeneration is caused by the anemia. The fatty change is best seen in the *heart*, which is pale, very flabby, so that it collapses when held up by the apex, and the wall of the left ventricle and the papillary muscles show a yellow speckling known as the "thrush breast" or "faded leaf" appearance (Fig. 180, page 330). This is marked when the anemia is severe, but may be slight or absent if death occurs during a remission. The *liver* shows two changes: fatty degeneration and siderosis. The fatty change may be extreme. The yellow granules of hemosiderin, which give the Prussian blue reaction for iron, are mainly deposited in the liver cells, especially in the outer two-thirds of the lobule. They are present, but to a lesser degree, in the Kupffer cells. Myeloid areas may be present; these are discussed below. The *spleen* is usually slightly enlarged; during a relapse it may be red and markedly swollen. The chief microscopic change is evidence of marked phagocytic activity on the part of the reticulo-endothelial cells, which contain pigment and fragments of red blood cells. These changes are most pronounced during a relapse. There are also deposits of iron pigment, but the siderosis is not nearly so marked as in the liver. It is evident that though the spleen may play a part in destroying the red cells, it is the liver which stores the blood pigment. Small islands of myelocytes and nucleated red cells are occasionally present. The *lymph nodes* show no special change. In the *kidneys*, as in the liver, there is a combination of fatty degeneration and hemosiderosis. This combination may be seen in lesser degree in many of the other organs.

The *bone-marrow* changes are by far the most important. There is a very marked erythroblastic reaction, as a result of which the yellow marrow becomes red and resembles red currant jelly. This change is patchy, so that examination of a small piece of marrow may be quite misleading. The marrow of one long bone may be red, while in another it is quite yellow, or the change may only affect part of the marrow of a bone. The hyperplasia always involves the femur before the tibia. During a remission the marrow of the tibia may be normal, while that of the femur shows marked hyperplasia. The earliest change is seen in the upper end of the femur and humerus, regions in which normally there is a certain amount of red marrow. As a result of the hyperplasia the trabeculae of the medullary cavity are absorbed and the cavity may be enlarged at the expense of the shaft.

The microscopic picture is quite different from that of the functional hyperplasia which follows hemorrhage. The latter is a normoblastic reaction, whereas the reaction in pernicious anemia is of the megaloblastic (Ehrlich) type (Fig. 440). The megaloblast changes directly into a macrocyte, with loss of the normal multiplication which should occur at the normoblastic level. Megaloblasts have no place in the development of normal red blood cells in extra-uterine life, but only when the normal activity of the hemopoietic principle of the liver is lacking. This explains the drop in the red cell count and the relatively few normoblasts in the circulatory blood. This reaction is the one and only pathognomonic finding in the

disease. During a remission there is a return to the normoblastic type of reaction. It must not be thought that the megaloblasts are the only cells of the hyperplastic marrow. Primitive white cells (myelocytes and myeloblasts) are always numerous, and at first sight it is remarkable that such numbers of primitive leucocytes in the marrow can be associated with a marked leucopenia. The answer to the riddle is that the white cells, like the red cells, fail to mature, and until they mature they are unable to enter the circulation. It looks as if some factor (possibly a liver factor) which is normally responsible for the maturation of myelocytes into polymorphonuclears is lacking in pernicious anemia. Adult polymorphonuclears are much less numerous in the marrow of pernicious anemia than in the normal marrow. The megakaryocytes are reduced in number, and those which are present are small and degenerated; this explains the thrombocytopenia. Phagocytic cells containing hemosiderin or erythrocytes are prominent during a relapse.

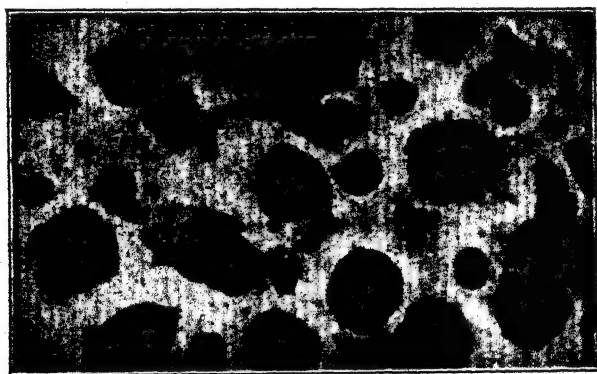


FIG. 440.—Megaloblastic reaction of the bone-marrow in pernicious anemia. All of the cells are either megaloblasts or normoblasts.  $\times 1000$ .

*Extramedullary blood formation* may occur, but it is difficult to know to what extent. Before the fifth month of fetal life the blood is formed by the liver and spleen. When there is great demand for more blood in pernicious anemia small islands of myeloid tissue may develop in the liver and possibly in the spleen. It is doubtful if these extramedullary foci play a part of any importance, for even in severe exacerbations it will seldom be found that all the bone-marrow of the body is hyperplastic.

The lesions of the *alimentary tract* affect chiefly the tongue and stomach. Soreness of the tongue is a frequent feature of the early stage of the disease. At the time of death there may be a severe glossitis, the tongue being fiery red and resembling a beefsteak. In more chronic cases the tongue is atrophic and smooth as if it had been ironed, with disappearance of the papillæ and atrophy of mucous membrane and muscle. It has been suggested that the tongue lesions are a manifestation of avitaminosis, because rather similar lesions can be produced in animals by means of deficient diets. The upper two-thirds of the stomach show severe atrophy; in some

cases the wall may be no thicker than parchment, so that the diagnosis may be made with the naked eye. The atrophy involves all of the coats (Fig. 441), and in the mucosa the specialized oxyntic and peptic cells have disappeared. At the junction of fundus with pyloric mucosa there is an abrupt change to normal thickness. The mucosal changes probably have an etiological relationship to the anemia. The mucosal changes in pernicious anemia may be precancerous in nature; in about 10 per cent of the cases carcinoma of the stomach subsequently develops.



FIG. 441.—Comparison of normal stomach wall (A) with that of pernicious anemia (B).  
× 65.

*Spinal cord lesions* occur in about 5 per cent of the cases. It is a sub-acute combined degeneration, affecting both posterior and lateral columns, more especially the former. The cord is swollen, and shows translucent patches first in the posterior columns, then the lateral columns, and finally the anterior columns. *Microscopically* there is breaking up and degeneration of the medullary sheaths, followed later by disappearance of the axis cylinders. The lesions are shown by means of the Weigert myelin sheath stain (Fig. 485, page 856). These changes are responsible for the ataxia and spasticity already described. The cord lesions bear no relation to the severity of the anemia, and may appear before any anemia can be detected. Nor are they responsible for the numbness, tingling, and paresthesias which are so common an accompaniment of the anemia.

**Nature of the Disease.**—The normal development of red blood cells in the marrow depends on a maturation or anti-pernicious-anemia principle. In pernicious anemia the marrow is packed with immature cells which are

unable to enter the blood stream in any numbers. To borrow a catchword from the political economist, there is poverty in the midst of plenty. The maturation principle is formed, as suggested by Castle, by the action of a gastric enzyme (the intrinsic factor) on a food protein (the extrinsic factor). The intrinsic factor is not the acid nor the pepsin of the gastric juice, but some specific factor so far unrecognized. The absence of this factor is associated with achlorhydria, although there may be no free acid in the gastric juice for many years before the development of anemia. Other members of the family may show achylia without anemia, indicating the hereditary character of the defect. The basis of the change may be the atrophy of the gastric mucosa. The argentaffin cells of the stomach, which are present in the pyloric and cardiac portions but not in the fundus, are completely or almost completely absent in pernicious anemia (Jacobson).

The maturation factor is stored in the stomach and liver, and is the active principle of liver extracts. It is a vitamin which was isolated from liver extract by Rickes in 1948 and was named B<sub>12</sub>. It is a growth factor, similar to the growth promoting factor found previously in fish solubles and cow manure, and influences the growth of micro-organisms in unbelievably high dilution. It is effective in the treatment of pernicious anemia in minute quantities, and has also been used for failure in growth in children. The principle can be separated by paper chromatography. Another member of the vitamin B group, pteroylglutamic acid, commonly known as folic acid, is also a growth factor which provides a powerful stimulus for maturation and is used in the treatment of pernicious anemia. B<sub>12</sub> has the great advantage of preventing the development of central nervous system lesions and of clearing them up when they have developed, whereas folic acid has no effect. It would appear that the spinal cord lesions are also due to a vitamin deficiency. The macrocytic anemia of pregnancy responds poorly to B<sub>12</sub>, but very well to folic acid. Deficiency in folic acid can be induced in the experimental animal by means of succinyl-sulphathiazole, which inhibits the bacterial synthesis of folic acid in the intestine. This leads to macrocytic anemia and severe granulocytopenia, with progressive hypoplasia of both the erythroid and myeloid elements of the marrow (Endicott *et al.*).

Other macrocytic anemias must be mentioned before closing this discussion. Of these the most important are the anemia of sprue, of *Dibothriocephalus latus*, and of pregnancy. *Sprue* is a tropical intestinal infection characterized by abdominal distention, the passage of large pale bulky stools with a high fat content, atrophy of the tongue and the intestinal mucous membrane, gastric anacidity in about one-half the cases, and the development of a blood picture which may be indistinguishable from that of pernicious anemia. The anemia is macrocytic and the reaction of the marrow is megaloblastic in type. It seems probable that the intestinal lesions (thinning and atrophy of the mucosa, disappearance of the epithelium) may so interfere with absorption that a condition of chronic deficiency develops, with the same effect on the marrow as in pernicious anemia. Other tropical macrocytic anemias are due to lack of the extrinsic factor in the food of poorly nourished natives. *Dibothriocephalus latus* is a common parasite among fish-eating peoples. A very small percentage

of such infected persons develop a macrocytic anemia identical with pernicious anemia. Achlorhydria is present in over 80 per cent of these patients. If the worm is expelled, the patient is cured, but the blood can be brought back to normal by means of liver treatment, even though the worm is still present in the bowel. Some additional factor besides the worm must be necessary to produce the anemia, possibly absence of something akin to the pernicious anemia-preventing principle. Fish tapeworm infestation is very common in Japan but is never associated with anemia, and pernicious anemia is also unknown in that country. Most of the cases of *Dibothriocephalus* anemia occur in Finland, suggesting that there may be some racial factor. In *pregnancy* a small number of women develop an anemia identical with pernicious anemia during the later months of pregnancy and in the early puerperium (this must not be confused with the common hypochromic anemia of pregnancy). It responds in the usual way to liver treatment, and the prognosis is much better than in pernicious anemia. *Gastrectomy* may be followed by macrocytic anemia if the acid-bearing part of the stomach has been removed. Only a few cases of gastrectomy develop the anemia, and a long interval elapses between the gastrectomy and the change in the blood picture. Diffuse disease of the liver such as *cirrhosis* may interfere so much with storage of the hemopoietic principle that the same type of anemia may sometimes develop.

**Iron-deficiency Anemias.**—Any anemia which responds to adequate doses of iron may be classed as an iron-deficiency anemia. The total amount of hemoglobin is low, but the red blood cells are not diminished in equal proportion, so that the color-index is low and the anemia is *hypochromic*. The red cells may be smaller than normal (*microcytic anemia*) or of normal size. There are two supplies of iron for the manufacture of hemoglobin: (1) the food, and (2) the iron stores in the liver, spleen and bone-marrow. In health only minute quantities of iron are absorbed, but in experimental iron-deficiency large amounts are absorbed. The course of the iron can be followed by rendering it radio-active and thus labelling it (Hahn). Absorption occurs mainly from the duodenum, and as this is dependent on gastric acidity it is evident that achlorhydria will often be associated with hypochromic anemia.

Iron-deficiency anemia may be caused: (1) by blood loss, (2) by deficient iron intake, and (3) by a demand so great that absorption and the iron stores are unable to satisfy it. *Blood-loss* factor needs continual emphasis. A man may slowly lose half his blood and make it up again, but in doing so he has exhausted his store of iron, and any further loss of blood will produce anemia. Gastric and uterine hemorrhage are common causes of continued blood loss. *Deficient intake* may be due to poverty, faulty dietary habits, or organic disease of the stomach and esophagus. *Excessive demand* is physiological and depends on age and sex. There is an increased demand for iron during the first two years of life, and on account of menstruation, pregnancy and lactation. For these reasons hypochromic anemia is common in infancy and in women during the reproductive period. Bottle-fed babies get an infinitesimal amount of iron, and prematurity may have prevented the accumulation of a sufficient store of iron.



**PRIMARY HYPOCHROMIC ANEMIA.**—Many names have been given to this condition, *e. g.*, idiopathic hypochromia, simple achlorhydric anemia, chronic chlorosis, etc. The condition is a disease of middle-aged women, among whom it is a more common cause of ill-health than pernicious anemia. It often follows pregnancy, or rather the anemia is a continuation of the anemia which normally occurs in the later months of pregnancy. Occasionally it may occur in men. It is remarkable for its chronicity, an average period being ten years. The patient presents a curious combination of the clinical picture of pernicious anemia and the blood picture of hypochromic anemia. Digestive symptoms are marked. There is evidence of gastritis—poor appetite, frequent absence of free hydrochloric acid in the stomach, and much mucus in the stomach contents so that the gastric juice is very viscid. The tongue is bald and glazed even more commonly than in pernicious anemia; in the severe cases it is angry and red. The nails often present a very characteristic appearance; they are dry and brittle, longitudinally striated, and turned up at the edges so that they become “spoon-shaped,” a change never seen in pernicious anemia. Paresthesias such as numbness and tingling may be present in the arms and legs. The spleen is often palpable, but is never greatly enlarged. The triad characteristic of the disease is anemia, atrophy of the mucous membrane of the tongue, and brittleness or spoon-shaped deformity of the nails.

The *blood changes* are the reverse of those of pernicious anemia, although the symptomatology is so similar. In pernicious anemia the anemia is hyperchromic in type, but in this condition it is achromic. In the former disease the bone-marrow reaction is megaloblastic, and in the latter it is normoblastic. The red cells are diminished in number, but the decrease in hemoglobin is still greater, so that the color index is low and hypochromia (achromia) is marked (Plate XXVa. and Fig. 443). The average diameter of the red cells is smaller than normal, while in pernicious anemia it is greater than normal (Fig. 442). It is therefore a *microcytic anemia*. There is no evidence of hemolysis (tingeing of the blood serum with bilirubin), as compared with the hemolysis characteristic of pernicious anemia. There is leucopenia, relative lymphocytosis, and thrombocytopenia.

The *cause* of the condition is an iron deficiency, as a result of which (1) the stimulus necessary for the normal maturation of the normoblasts is lacking, so that they are unable to develop into erythrocytes quickly enough, and (2) the hemoglobin molecule is not properly built up in the normoblasts. The result is a stuffing of the marrow with normoblasts, and a deficiency of red cells in the blood, those present being poorly supplied with hemoglobin. The basis of the deficiency appears to be failure in the absorption of iron, which in turn is due, at least in part, to the hypochlorhydria, as the presence of acid is necessary for the solution and absorption of iron. The administration of large amounts of iron, especially when combined with small amounts of copper, has the same dramatic effect as liver treatment in pernicious anemia. The reason for the massive doses of iron far in excess of the needs of the body (the total amount in the body is about 3 grams or the amount in a large nail) appears to be that solubility, greatly diminished by the absence of acid, is accelerated by the presence of excess of iron. One form of hypochromic anemia among the

poorer classes is due to a lack of iron in the diet, particularly in women in relation to pregnancy and menstruation. Anemia in young children may be of this type, as milk is poor in iron. Sex is an important factor, because of the loss of menstrual blood and the fact that during pregnancy much of the maternal iron is stored in the fetus.

The so-called *Plummer-Vinson syndrome* is practically the same disease with the addition of dysphagia. It occurs in middle-aged women, although occasionally in men, and is characterized by hypochromic anemia, dysphagia, dryness and atrophy of the mucous membrane of the tongue, pharynx, and esophagus, painful cracks at the angles of the mouth, achlorhydria, brittleness of the nails, and enlargement of the spleen. There is

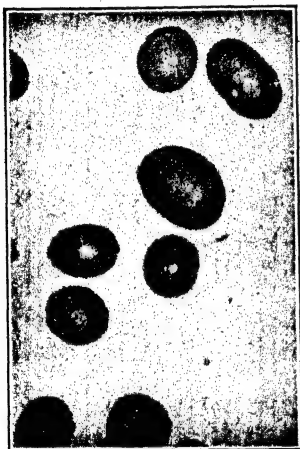


FIG. 442

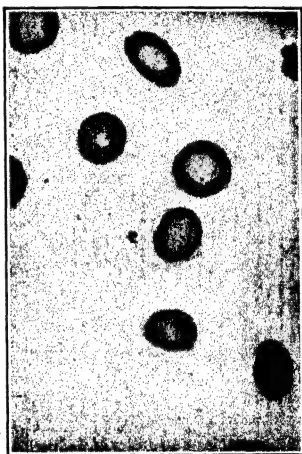


FIG. 443

FIG. 442.—Hyperchromic anemia (pernicious anemia). The cells are macrocytic.  $\times 1000$ .

FIG. 443.—Hypochromic anemia. The cells are microcytic.  $\times 1000$ .

a tendency for the condition to act as a predisposing cause of cancer of the hypopharynx in women. Owing to the dysphagia the patient will be found to have been living on slops for a prolonged period, and the anemia is doubtless due to the deficiency of iron in the diet. It responds remarkably to the administration of iron.

**PYRIDOXINE DEFICIENCY ANEMIA.**—An interesting link between the two principal forms of nutritional anemia in man, namely, pernicious anemia and iron-deficiency anemia, is provided by experimental pyridoxine deficiency anemia in swine (Wintrobe, *et al.*). When the diet of the pig is lacking in pyridoxine but adequate in all the other elements of the vitamin B complex, the animal develops a severe anemia characterized by microcytosis, polychromatophilia, reticulocytes and nucleated red cells in the blood, a rise in the serum iron, hemosiderosis and bone-marrow hyperplasia. The microcytic anemia resembles that due to iron deficiency, whilst the hemosiderosis and elevated serum iron suggest pernicious

anemia. It is evident that in the pig pyridoxine plays some essential part in erythropoiesis and the synthesis of hemoglobin.

**ANEMIA OF INFECTION.**—Anemia is a feature of many chronic infections, a striking example being subacute bacterial endocarditis. It seems probable that the anemia is due to some abnormality of hemoglobin synthesis apparently dependent on the presence of infection rather than to hemolysis or aplasia of the marrow. Such anemias are refractory to iron and liver therapy. Wintrobe and his associates have shown that in this condition the plasma iron is very much below normal, nor does the administration of iron raise the plasma iron as it does in the normal person. There appears to be a failure in the utilization of iron for hemoglobin regeneration during chronic infections due probably to some unknown "persistent and urgent demand for iron to fulfill some function in relation to infection which has a greater priority for iron than hemoglobin formation." There is reason to believe that iron accumulates in inflammatory tissue and in the reticulo-endothelial system in experimental infections.

In reviewing the various forms of nutritional anemia it seems justifiable to say that they are all due to some form of deficiency. (1) The deficiency may be in the food. (2) The food may be adequate, but the stomach may be unable to utilize what is presented to it, the most obvious example being cases of gastrectomy. And finally (3) the defect may be in the liver. In pernicious anemia there is an abundance, indeed a surplus, of hemoglobin pigment and iron; the real lack seems to be in the constituents of the stroma of the red cells. The cells are therefore hyperchromic. In the hypochromic anemias, on the other hand, there is a deficiency of iron and the hemoglobin molecule is not properly formed.

### APLASTIC ANEMIAS

Aplastic anemia may be primary or secondary. The *primary form* is fortunately a rare disease occurring in young people usually between the ages of fifteen and thirty years. It may be very acute and extremely fatal, killing the patient in a few weeks, or at the most some months. Fever is very common, due probably to interference with the heat regulating mechanism. The cause is unknown. Some agent depresses the activity of the bone-marrow until no more blood is formed. The normal amount of blood destruction is going on, but there is nothing to take the place of the destroyed erythrocytes. The anemia becomes extreme, but the blood film remains strangely normal; there are none of the changes such as the presence of macrocytes, nucleated red cells, polychromatophilia, reticulocytes, etc., which indicate that the marrow is struggling to make good the wastage. All the formed elements of the blood are diminished, the leucocytes and platelets as well as the red cells. On account of the extreme thrombocytopenia purpuric hemorrhages form an important feature of the clinical picture, and it may be very difficult to distinguish the condition from true purpura hæmorrhagica. The color index is below normal, but not extremely low. There is no evidence of hemolysis such as an increase of bilirubin in the blood or the appearance of urobilinogen in the urine. The red bone-marrow is profoundly aplastic, consisting of little more than fat, and contains very few cells (Fig. 444), but some islands of hyperplasia may be found.

The *secondary* form of aplastic anemia is usually due to exhaustion of the marrow. In the end-stage of pernicious anemia the marrow may give up the fight, so that no hyperplasia may be found at autopsy and regeneration forms of red cells are absent from the blood. Severe and continued toxic conditions, poisons such as benzol and trinitrotoluol, and roentgen-rays may all injure the marrow so severely as to lead to an aplastic form of anemia. Severe and even fatal aplastic anemia may be caused in susceptible persons by the long-continued use of chloromycetin. Myelophthisic anemia is a variety of secondary aplastic anemia in which the erythrogenic tissue of the marrow is replaced by tumor growth. This may be primary (multiple myeloma, Ewing's tumor) or secondary (carcinoma of the breast,

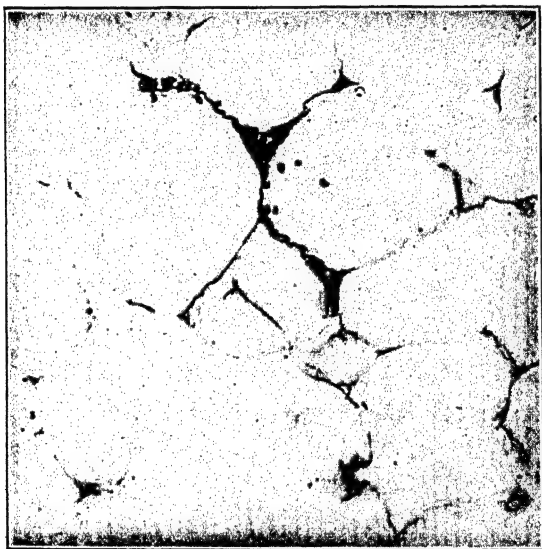


FIG. 444.—Bone-marrow in aplastic anemia, showing complete absence of hyperplasia.  
× 275.

prostate, kidney, lung, thyroid). In the rare condition known as osteosclerosis in which the bone is thickened and the marrow reduced, an aplastic anemia (osteosclerotic anemia) may develop. The lesion to which the descriptive name of *myelosclerosis* is applied, of unknown etiology, produces a similar blood picture. In carcinomatosis of the bone-marrow there may be a picture of leuco-erythroblastic anemia, i. e., nucleated red cells and myelocytes appear in the blood even when the anemia is slight; the anemia may be hemolytic in type (Waugh). These features may be of diagnostic importance.

**SECONDARY ANEMIA.**—Not so long ago one of the main groups of the anemias was that known as secondary. This term may well be given up. It signified the anemias due to loss of blood and those associated with interference with blood formation owing to direct injury to the red marrow or to constitutional diseases such as nephritis, subacute and chronic infections, and cancer. The former is a hypo-

chromic microcytic anemia and the latter a normochromic normocytic anemia. Neither is benefited in the slightest by liver or iron therapy.

### THE HEMOLYTIC ANEMIAS

The hemolytic anemias may be divided into primary, or idiopathic, and secondary groups. In the secondary group hemolysis occurs as the result of snakebite, malaria, and infection with hemolytic streptococci, and it forms a characteristic feature of pernicious anemia. The chief members of the primary group are hemolytic jaundice, sickle-cell anemia, and erythroblastic anemia. To these may be added paroxysmal hemoglobinuria.

Hemolytic anemia is the result of excessive destruction of red blood cells and is accompanied by evidence of increased regeneration of red cells. The mechanism of destruction may be one of two profoundly different types. (1) The red cells may be of faulty construction so that they are readily destroyed. The defect is transmitted by a gene, so that this is the *hereditary type*, although it is commonly wrongly referred to as congenital which signifies being present at birth but not necessarily gene-produced. Examples of these intracorpuseular defects are hereditary spherocytic anemia, sickle cell anemia and Mediterranean anemia. The Coombs test is negative. (2) In the second group the red blood cells are normal when produced, but they are altered by acquired abnormal factors (hemolytic antibodies in many cases), so that they are destroyed in excessive numbers. This is the *acquired type* of hemolytic anemia which is the more common of the two. The Coombs test is frequently positive. The acquired group includes cases which may be described as idiopathic with circulating antibodies and spherocytes (probably the commonest variety of hemolytic anemia), erythroblastosis fetalis and the paroxysmal hemoglobinuria associated with exposure to cold. At least some of the anemia of neoplastic diseases such as the malignant lymphomas, leukemia and carcinoma may be of this type, as circulating hemolysins have been demonstrated in the blood in a number of cases, and the survival time of transfused red cells is markedly decreased. It is of interest to note that abundant intracytoplasmic acidophilic bodies giving a strongly positive reaction with the periodic acid-Schiff method have been found in neoplastic lymphocytes in the lymphoid tissues in cases of lymphatic leukemia and lymphosarcoma (Rappaport). This raises the question as to whether the neoplastic lymphocytes may not be connected in some way with the production of the auto-antibodies responsible for the Coombs reaction which is positive in these cases.

The Coombs test is designed to show the presence of antibodies (agglutinins) adsorbed to the surface of the red cells in the acquired but not in the hereditary forms. A rabbit is immunized with human serum globulin, a human globulin antiserum being produced in the rabbit. When the red cells of the patient are tested with this serum there is agglutination only in the acquired form.

Hemolysis with hemolytic anemia may be caused by the action of readily recognized exogenous hemolytic agents. Among such agents are snake

venom, a variety of drugs (phenacetin, acetanilide, sulpha compounds), and infection with hemolytic streptococci, the malaria parasite, etc.

Normal red cells can be tagged with an isotope such as radioactive iron. Their life varies from one hundred to one hundred twenty days. When the red cells (spherocytes) of a patient with congenital hemolytic anemia are injected into the circulation of a normal person they disappear completely within fourteen to nineteen days. On the other hand, normal red cells are rapidly destroyed by patients with acquired hemolytic anemia, whereas cells of acquired hemolytic anemia survive normally when transfused into normal persons. This indicates that in the congenital form the fault lies in the red cells, whereas in the acquired form it lies in the environment.

**Hereditary Spherocytic Anemia.**—The basic hereditary defect is the spheroidal shape of the erythrocytes in place of the normal biconcave discs. This is responsible for increased fragility of these cells, and the excessive blood destruction gives rise to a hemolytic jaundice, also known as acholuric jaundice because no bile appears in the urine. So striking is this feature that a common name for the condition is congenital hemolytic jaundice. The most precise name for the blood dyscrasia would be hereditary spherocytosis, because there may be spherocytosis without either anemia or jaundice. It must be noted that spherocytes are also found in acquired hemolytic anemias, but here they are not gene-induced.

Hereditary spherocytic anemia is familial and usually congenital, though it may not manifest itself until the second decade. One case is reported in which the disease remained latent until the age of seventy-five years, when treatment by splenectomy was successful (Mandelbaum). Some members of the family may have fragile red cells, but no anemia or jaundice. The jaundice persists throughout life, usually in mild form but with occasional exacerbations due to the characteristic "crises," in which there is increased blood destruction with attacks of pain in the region of the liver and spleen. This is in reality the result of an acute aplastic condition in the erythropoietic tissue with complete cessation of formation of red cells (Owren). As the average lifetime of the red cells in this disease is only fifteen days (compared with the normal one hundred twenty days) it is evident that an acute crisis may be expected when the cells cease to be formed. The jaundice is due to increased production of bilirubin owing to excessive blood destruction. There is therefore an excess of bilirubin in the stools, increased production of urobilinogen, which is excreted in the urine, but bilirubin does not appear in the urine, hence the name acholuric jaundice. The blood gives an indirect van den Bergh reaction. Gall stones of the pure bilirubin type without any admixture of cholesterol are frequently present. The spleen is considerably enlarged. The long bones show longitudinal striation and a patchy moth-eaten appearance in the roentgen-ray picture, owing to osteoporosis produced by the hyperplastic marrow.

The blood shows a secondary anemia, usually mild, but severe in the crises. The patient may have a count as low as 3,000,000, and yet be without symptoms and able to play his part in the world. If the anemia becomes severe it may closely resemble the pernicious anemia type. The

two chief characteristics of the film are microspherulocytes and reticulocytes. A spherocyte is smaller and thicker than normal; it is spherical instead of biconcave. This characteristic can be recognized in wet preparations; in dry smears the cells merely appear as densely stained microcytes. Haden has shown that this increase in thickness is related to the increased fragility (see below), and that microspherocytosis is the fundamental in-born error in hereditary hemolytic anemia. As biconcave cells become globular when placed in hypotonic saline, it is evident that the more globular cells will rupture more readily. "The anemia, jaundice, splenomegaly, reticulocytosis and increased fragility are all secondary to the globular form of the erythrocyte" (Haden). Reticulated red cells are more numerous than in any other disease. In place of the usual 1 per cent there may be 20 per cent; in the acquired form there may be 50 per cent or more. This is an indication of compensatory bone-marrow activity. The white cells share in this activity, and the leucocyte count is generally from 12,000 to 15,000. In crises it may go up to 80,000. Normoblasts may be numerous, and these may be mistaken for leucocytes in the counting chamber and cause error in the count. There is an increased fragility of the red cells, *i. e.*, they are hemolyzed by salt solution of a strength which leaves normal red cells untouched. It is only the small spherical cells which are abnormally fragile, and these are selectively removed by the spleen where they are found in large numbers.

LESIONS.—The most striking change is in the spleen, which is markedly enlarged and weighs about 1000 grams. It is firm and of a bright red color like a beefsteak. It is stuffed with blood, so that after removal it loses considerably in bulk unless the vessels are clamped. The capsule is thickened. *Microscopically* the pulp is entirely occupied by red cells, thus presenting a very characteristic appearance. The sinuses are empty, and the lining cells may resemble glandular epithelium. The phagocytic cells contain a large amount of hemosiderin, especially during the hemolytic crises. The other reticulo-endothelial organs (liver and bone-marrow) also show hemosiderosis, as do the epithelial cells of the liver and kidney. Hemosiderosis may occur in any condition associated with long-continued hemolysis. Repeated blood transfusions may give a picture simulating hemochromatosis, but only when the number of transfusions exceeds one hundred. In course of time a marked degree of fibrosis may develop in the liver and pancreas as well as in other organs, so that it may be difficult or indeed impossible to distinguish the lesions from those of hemochromatosis without a knowledge of the condition of the blood. In Mediterranean (Cooley's) anemia this fibrosis is seen when hemolysis has been going on for many years, but never in young children (Ellis *et al.*).

THE RELATION OF SYMPTOMS TO LESIONS.—The essential symptoms are anemia and jaundice; the essential lesions are splenomegaly and hemosiderosis. The connecting link between the two groups is the increased fragility of the red cells, which itself is due to spherulocytosis. Owing to this fragility the red cells are unduly exposed to the inimical influence of the reticulo-endothelial cells, particularly those of the spleen, and are thereby broken down. Removal of the spleen removes one of the chief destructive agents and thus produces a clinical cure. "The hemolytic diseases are the children and the spleen is their mother, but the father is still

unknown and possibly there are several fathers." The presence of bilirubin calculi is to be explained by the excess of bilirubin in the blood and in the bile. The acholuria is due to the fact that the hemolytic type of bilirubin is unable to pass through the renal filter.

**HYPERSPLENISM.**—This is the term applied to a hypothesis designed to explain an association of splenic enlargement with marked diminution in the circulating blood of erythrocytes (congenital hemolytic icterus), platelets (thrombocytopenic purpura), granulocytes (splenic neutropenia), or all three (panhematopenia). As Wiseman and Doan put it: "The reticulo-endothelial cells of the spleen when on a rampage of destruction may selectively choose as victim any *one* of the elements of marrow origin passing through this organ, but more often than not other innocent bystanding elements suffer likewise in some degree. Splenectomy always is followed by an increase in *all* circulating blood elements whenever applied in any one of these conditions." Two explanations have been offered for this association of splenomegaly with depression in the formed elements of the blood. The first, championed particularly by Dameshek, is that of *marrow inhibition*. The spleen is believed to depress marrow function by some influence, probably hormonal. The second view is that of *splenic hypersequestration*. The fact that splenectomy produces immediate improvement in the blood picture, and that marrow hyperplasia is a feature of the syndrome, appears to favor the second view. The unique anatomical arrangements of the spleen, with its combination of a smooth muscle capsule, pulp, and large fenestrated sinusoids, provide an ideal reservoir for blood storage. "The human spleen has a semi-open circulation controlled by a filter-mesh mechanism in the sinus wall which by heredity or under pathological conditions may become more or less permeable to blood" (Doan). There is abnormal stasis in the sinusoids or pulp and loss of plasma and erythrocyte potassium. This leads to increased fragility of the red cells, and exposes them to the phagocytic activity of the reticulo-endothelial cells, an ideal environment for cell destruction. The principal microscopic change is a prominent marginal zone of the Malpighian follicles (Leffler). In addition to the primary hypersplenism which has just been described there is a less common *secondary form*, which may give the same picture of specific splenic sequestration. This is seen in such conditions as Banti's, Gaucher's, and Hodgkin's disease, sarcoidosis, and tuberculosis of the spleen.

**SICKLE-CELL ANEMIA.**—This condition bears such a strong resemblance to hereditary hemolytic anemia that the two should be considered together. Both are familial and hereditary. Both are characterized by a hemolytic type of anemia, acholuric jaundice, hemosiderosis, and the appearance of large numbers of reticulocytes. In both there is some defect in the composition of the red cells. Splenectomy may cure the clinical symptoms of both, but in neither is the underlying weakness improved, in the one case the spherical character of the red cells, in the other the sickle-shaped deformity of these cells. The disease is apparently confined to the Negro, but the white man may show a tendency to sickle-cell formation. In the Negro the disease may show an active or a latent phase, the latter representing the sickle-cell tendency. The *active phase* is marked by a fairly severe anemia, leucocytosis, hemolytic jaundice, increase of bilirubin in the blood and of urobilinogen in the urine. The film may show large numbers of crescentic or sickle-shaped red cells (Fig. 445), and many reticulocytes. Sickle cells can be shown in the *latent phase* by keeping a moist film sealed for a number of hours; as the oxygen tension diminishes the red cells become distorted and sickle-shaped. Moreover it is the exception, not the rule, for active cases to show numerous sickle cells, although tailed and pointed forms are present. Countless cases have been missed in the past through lack of use of the moist film. In addition to the blood changes the active stage may be marked by fever, joint and muscle pains, and enlargement of the spleen and liver. Chronic ulcers are very common in the lower half of the leg.



The *lesions* are indefinite. There may be pools of blood around the Malpighian bodies of the spleen, due in Rich's opinion to a congenital malformation of the sinuses. There is a general siderosis as well as siderotic nodules in the spleen. The red cells in the vessels are distorted. Osteoporosis may be present.

**MEDITERRANEAN ANEMIA (THALASSEMIA).**—This disease goes by a variety of names, of which mention need only be made of Cooley's anemia, erythroblastic anemia and leptocytosis. It is characterized by a constant familial and racial incidence, a typical facial appearance, distinctive changes in the bones, and enlargement of the spleen. It usually appears in the first two years of life and sometimes in the newborn. The familial (hereditary) incidence is marked: it has been reported in identical twins. It is a disease of the Mediterranean races, most often in Greeks, but also in Italians and Armenians. The skin is yellow, the face mongoloid, the head enlarged, the abdomen prominent, the stature stunted. Owing to hyperplasia of the marrow the bones show medullary trabeculations in the roentgen ray picture, and the skull is thickened by the thick diploe. There is a moderate or marked anemia, the platelets are increased, and there is a leucocytosis which may reach 50,000. The characteristic features of the blood film are the great numbers of erythroblasts and the presence of leptocytes or thin cells (*leptos*, thin), oval cells and target cells. The leptocytes are comparable to the sickle cells, both representing a departure from the normal. Target cells are so called because they are characterized by a central area of condensed hemoglobin, which is surrounded by a pale zone, the periphery again being dense. The entire effect has been likened to a Mexican hat. Target cells are not confined to Mediterranean anemia. Indeed they are more likely to be seen in cases of cirrhosis of the liver and after splenectomy. The pathognomonic feature is the presence of great numbers of nucleated red cells, both normoblasts and megaloblasts. In one case in the newborn there were 90 per cent of erythroblasts. The immature red cells suffer at the hands of the reticulo-endothelial cells, which accounts for the anemia and the deposits of hemosiderin in the spleen, liver, pancreas, and other viscera, almost like hemosiderin. Excessive erythropoiesis is present in the marrow and in the spleen and liver. The course is usually chronic and may last a number of years.

**PAROXYSMAL HEMOGLOBINURIA.**—This rare condition is characterized by sudden attacks of fever and chills accompanied by the appearance of hemoglobin in the urine. There are two etiological factors, *syphilis* and *exposure to cold*. The exposure to cold may be very slight, such as washing the hands in cold water or even drinking cold water. Usually cold weather is needed, and the most bloody urine that I have seen was passed on a day of 60 degrees of frost. Shortly after exposure to cold the patient develops pain in the muscles and abdomen, followed by severe chills and fever. The urine is full of hemoglobin and may be of a port-wine color. It contains no well formed red cells, but numerous ghosts of hemolyzed cells; the urine is therefore clear, not smoky or cloudy as when it contains ordinary blood. The spectroscopic shows the absorption bands of oxyhemoglobin or methemoglobin. There may be transient jaundice, due to the formation of bilirubin from the liberated hemoglobin. The spleen may be temporarily enlarged. The blood shows a hemolytic

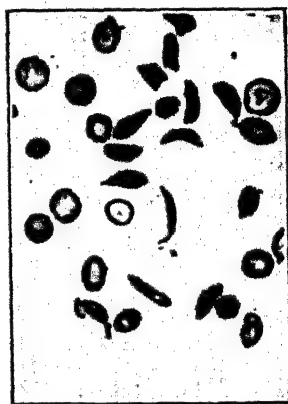


FIG. 445.—Sickle-cell anemia. Many erythrocytes are sickle-shaped.  $\times 500$ .

anemia, followed by very rapid regeneration. There is a transient leucopenia due to the protein shock caused by the rapid liberation of hemoglobin.

The hemolysis is due to the presence of an autohemolysin which is present in the blood of some syphilitic patients. This unites with red blood cells in the presence of complement but strange to say, only at a low temperature. When the two factors of syphilitic hemolysin and a low temperature are both present, a sudden reaction takes place with marked hemolysis and the liberation of large quantities of hemoglobin in the blood. This causes transient hemolytic jaundice and is excreted in the urine giving hemoglobinuria. Hemolysis with hemoglobinemia and hemoglobinuria may be caused by malaria, by drugs of the coal-tar series, or by blood transfusion, but in these cases the mechanism is quite different and bears no relation to cold.

The *nocturnal Marchiafava-Micheli type* of paroxysmal hemoglobinuria occurs only during sleep or is more marked at that time. The morning urine is deeply colored. The red cells are abnormally susceptible to hemolysis in plasma of increased acidity such as results from reduced pulmonary ventilation during sleep. *March hemoglobinuria* occurs on physical exertion such as short brisk walks; it has been observed particularly in soldiers.

**Congenital Hemolytic Disease.**—Hemolytic disease of the newborn is due to a reaction between the Rh factor which acts as an antigen in the red blood cells of the fetus and corresponding agglutinating antibodies which reach the fetal blood from the maternal circulation. It is an interaction of fetal antigens and maternal antibodies. The disease may take various forms, which are known by such names as congenital anemia, erythroblastosis fetalis, icterus gravis, and hydrops fetalis. The condition is essentially an Rh incompatibility, a term more descriptive than the common designation erythroblastosis fetalis, for erythroblasts may be present in excess in the fetal blood and tissues as the result of other causes (Macklin).

The red blood cells of the majority of human beings contain an agglutino-gen known as the Rh factor. This is so called because a similar agglutino-gen was demonstrated in 1940 by Landsteiner and Wiener in the red cells of the rhesus monkey. It is the rhesus factor. The presence of the agglutino-gen in human red cells was then demonstrated by testing them against anti-rhesus serum. The presence of the Rh factor bears no relation to the blood group (using the word in the ordinary sense) to which the patient belongs. The Rh agglutino-gen is not a single substance, but consists of several antigens. It is possible to divide the Rh blood type into at least 10 subtypes and probably more. Reactions as the result of the various subtypes are fortunately rare. About 85 per cent of persons possess the Rh factor so that they are Rh-positive, whilst 15 per cent lack the factor and are Rh-negative. There is a racial distribution of the factor as indicated by the fact that 90 per cent of Negroes and 99 per cent of Chinese are Rh-positive. Anti-Rh agglutinins may be formed in Rh-negative persons following the transfusion of Rh-positive blood. An Rh-positive father can transmit the factor to the fetus as a simple Mendelian dominant. If the mother is Rh-negative, anti-Rh agglutinins may be formed in her blood as the result of immunization or sensitization by the Rh factor of the fetus (Fig. 446).

The stage is now set for disaster in two possible forms. (1) If the mother is transfused with Rh-positive blood, even though belonging to the same

general blood group, there may be an intra-group transfusion accident. (2) If the maternal anti-Rh agglutinins reach the fetal blood through the placenta, they will react with the agglutino-gen in the fetal red cells, as a result of which there will be a slow continuous hemolysis of those cells, although in the test tube the reaction takes the form of agglutination.

*The Rh Factor in Blood Transfusion.*—Intra-group blood transfusion reactions are usually due to the Rh factor. The danger arises if an Rh-negative person is transfused with Rh-positive blood a number of times. (In rare instances a single transfusion is sufficient.) Once sensitization occurs it appears to be permanently imprinted on the individual's constitution, and a further transfusion years later may be followed by a severe reaction. In women an initial transfusion is not necessary, provided they have become sensitized by having had an Rh-positive child. Thus Rh-negative women who have borne children should be transfused only with Rh-negative blood.

*The Rh Factor in Pregnancy.*—In pregnancy the presence of the Rh factor in the red cells of the fetus carries a twofold threat, first to the mother and secondly to the child. The former, the danger of a transfusion reaction due to the presence of Rh antibodies in the woman's blood, has already been discussed. In the child the threat is the development of hemolytic disease of the fetus and the newborn. The chance of dangerous consequences is not as great as might be feared, as will be evident from the following figures. One out of 12 marriages involves an Rh-positive husband

and an Rh-negative wife. The incidence of hemolytic disease of the infant is about 1 in 250 to 500 deliveries, that of the severe jaundiced form of erythroblastosis fetalis 1 in 1500 deliveries, and the fatal hydrops form 1 in 2000 deliveries. While the condition may arise in the first pregnancy, it may not develop until after the tenth normal child has been born. Not all mothers who are Rh-negative become sensitized by an Rh-positive fetus. The exact percentage who escape and the reason for this is unknown.

The child may be born dead, especially in the hydrops cases, it may live only a few days, or it may survive. About 7 per cent of those which survive are mental defectives. If jaundice develops it usually does not do so until some days after birth. This is apparently due to excretion of the excess of bilirubin through the placenta. In the most severe form of all, hydrops fetalis, jaundice is absent.

It sometimes happens that the titer of agglutinins in the maternal blood bears no relation to the severity of the hemolytic disease in the child. Indeed in the hydrops cases there may be an apparently complete absence

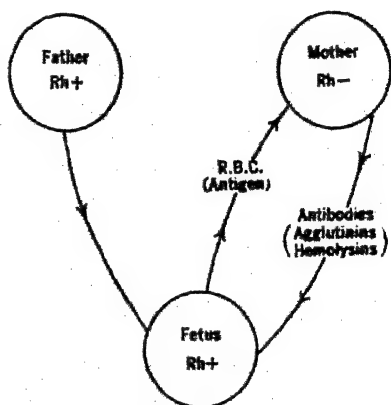


FIG. 446.—Diagram to illustrate Rh factor. (Courtesy of Dr. I. Erb.)

of maternal agglutinins. This paradox is explained by the discovery in the maternal serum of what have been called *blocking antibodies* in addition to the usual agglutinating antibodies. The blocking antibodies interfere with the union in the test tube between the antigens and the agglutinating antibodies, so that the presence of the latter is readily overlooked.

The *clinical picture* in the child is one of *congenital anemia* with *erythroblastosis fetalis*. Jaundice may or may not be present. There are great



FIG. 447.—Congenital hydrops in erythroblastosis fetalis.

numbers of nucleated red cells, a compensatory phenomenon, and active erythropoiesis in the liver and spleen, together with hemosiderosis in these and other organs. In a small number of cases there is necrosis of the liver, and still more rarely actual cirrhosis occurs (Craig). The child may die in the course of a few days of *malignant icterus neonatorum*. In such a case the nuclear structures of the brain show intense staining with bile ("Kernicterus"). It is estimated that brain damage associated with kernicterus is present in some 15 per cent of cases. About 70 per cent of the babies with this lesion die within seven days of birth, and those which do not die

are liable to have permanent neurologic sequelæ, such as cerebral palsy. The damage develops late in the second day, with opisthotonos as the characteristic symptom. It bears a close relation to the severity of the jaundice (Diamond). If the serum bilirubin is kept below 20 mg. per 100 cc. by means of exchange transfusion, this serious complication can be almost completely prevented. In *congenital hydrops* the child is likely to be born dead with edema and marked ascites (Fig. 447). The cause of the edema appears to be an increased permeability of the capillary walls due to anoxemia. The hydrops variety is associated with a greatly enlarged and edematous placenta, the surface being made up of large, friable, pale cotyledons. Microscopically the villi show evidence of immaturity, such as large size, the persistence of Langhans cells which normally disappear about the middle of pregnancy, and the presence of numerous erythroblasts in the capillaries. In the jaundiced form of erythroblastosis the changes in the placenta are similar but of much milder degree. If the fetus has died before the onset of labor and become macerated it may be very difficult to establish a diagnosis. Here again the presence of placental changes and of numerous erythroblasts in the pulmonary capillaries is of great value (Potter).

### PURPURA

Purpura is a condition in which there are hemorrhages in the skin and mucous membranes. It is a symptom or symptom-complex rather than a disease, and there are many varieties of purpura. Of these there is one which forms a definite disease entity which must be sharply differentiated from all the other varieties, and which is usually known as purpura hemorrhagica, or better, primary thrombocytopenic purpura.

**Thrombocytopenic Purpura.**—This condition, also called Werlhof's disease, was described by Werlhof in 1740, but it was not until 1910 that Duke demonstrated that the essential basis of the condition was a thrombocytopenia or decrease in the number of the blood platelets (thrombocytes).

**SYMPTOMS.**—The disease is commoner in young people of the female sex. The hemorrhages which form the chief clinical feature may be small petechiæ or large ecchymoses. There may be hemorrhages into the skin, hemorrhage from the mucous membrane of the nose, mouth, stomach, intestine, and uterus, and blood in the urine. The hemorrhage may be spontaneous or traumatic. Hemorrhage due to trauma may last for an hour or more; the bleeding-time is prolonged, but the clotting-time is normal. In hemophilia, on the other hand, the clotting-time is prolonged, but the bleeding-time is normal. A tourniquet applied to the arm so as to obstruct the venous but not the arterial flow causes petechiæ to appear below the tourniquet. The spleen may be moderately enlarged, and splenectomy may be attended by brilliant results. In this connection it must be recognized that the disease may follow an acute or a chronic course. The *acute* cases prove fatal in the course of a few weeks, and splenectomy is not of the slightest use. The *chronic* cases may go on for months or years, and for some unexplained reason there may be intermissions when the patient is free from all signs of the disease. It is in these cases that splenectomy gives the best results.

The most striking change in the blood is the thrombocytopenia. The normal number of platelets is 200,000 or 250,000 per c.mm. In purpura hemorrhagica the number is usually below 60,000, and in severe cases they may entirely disappear.

We can only guess at the cause of this remarkable disappearance. It seems probable that the platelets are defective in quality, just as are the red cells in hemolytic jaundice and sickle-cell anemia. They therefore fall an easy prey to the destructive and phagocytic powers of the reticulo-endothelial cells in the spleen, liver, bone-marrow, and lymph nodes. Splenectomy removes the largest collection of these cells, so that the fragile platelets are now able to hold their own. On the other hand a thrombocytopenic factor not of splenic origin has been demonstrated in the plasma of a number of these patients (Harrington *et al.*). When the plasma is injected into normal persons there is a prompt decrease in the number of platelets, often apparent within one hour and lasting nearly a week, due apparently to destruction of the platelets. The same result is obtained with the blood of patients from whom the spleen has been removed. The factor seems to be a constituent of the globulin fraction. It is possible to prepare an antiplatelet serum which when injected into an animal causes an extreme fall in the number of platelets with the appearance of purpuric symptoms. In some cases there may be no marked change in the platelet count, but in these there may be a qualitative change. In the general discussion of blood platelets we have seen that it is the small (young) platelets which are active in stopping bleeding, the larger ones being inactive. In purpura hemorrhagica there may be many large and giant platelets, but although giants morphologically they are dwarfs functionally.

The blood shows other changes. There is an anemia of varying severity, depending on the degree of the hemorrhage. Leucocytosis is present after the hemorrhages. The clotting-time is normal and the bleeding-time greatly prolonged. A very characteristic feature due to the absence of platelets is loss of contraction power of the clot, so that it is unable to shrink from the side of the test tube in which the blood is collected.

**LESIONS.**—The germinal centers of the lymph follicles in the spleen are large and active, so that they can readily be seen with the naked eye. The sinuses are nearly empty, and the lining cells are swollen and may resemble glandular epithelium. A characteristic finding is the presence of megakaryocytes in the sinuses of the spleen, and also in the liver sinusoids and other capillaries (Nickerson and Sunderland). Hyaline megakaryocytes which produce large pseudoplatelets are found only in this disease. It must be noted that, although the megakaryocytes are supposed to produce the platelets, very careful counts of these cells in the marrow fail to reveal the reduction in the number of these cells which might be expected.

**THE RELATION OF SYMPTOMS TO LESIONS.**—The main symptom is the hemorrhage, the main lesion thrombocytopenia. In discussing the relation between these two it is fundamental to distinguish between spontaneous hemorrhage and the hemorrhage which follows trauma, both of which are present in purpura. The prolonged bleeding-time after an incision is due to the lack of platelets. Hemorrhage from a vessel is first arrested not by the production of fibrin but by the formation of a plug of platelets which adhere together and close the hole temporarily until a permanent clot is produced. In the absence of the platelets this all-important clot cannot be formed. The platelets also initiate the process of clotting, for when they disintegrate owing to injury they liberate the necessary thromboplastin. Only a small number of platelets are necessary for this purpose, and there are sufficient in most cases of purpura, so that the coagulation-time is normal. The excess of platelets causes retraction of the clot in some unknown way. In purpura there is no excess, so that the clot in the test tube fails to retract.

The cause of the spontaneous hemorrhage, which after all is much more common and important than hemorrhage due to trauma, remains a mystery. Presumably

it bears some relation to the thrombocytopenia. It is as if the vascular pipes normally leaked, perhaps as the result of minimal trauma, but the leaks are continually plugged by the platelets. In thrombocytopenia such plugging is no longer possible. The long intermissions in the chronic cases are also difficult to explain. A final difficulty is the therapeutic effect of splenectomy. The theoretical basis for this form of treatment is the observation that removal of the spleen in a normal animal is followed by a marked rise in platelets. This occurs also in man, but in the course of a few weeks or months the platelets may fall again to their original level, and yet the patient may remain free from purpuric manifestations. There must be more in splenectomy than meets the eye. It is important to note that removal of the spleen may produce a temporary but not a permanent cure; the patient may remain well for a year or two, and then the purpuric manifestations may return. Cases should be followed for from three to five years before one can be certain that the condition is cured.

**THROMBOTIC THROMBOCYTOPENIC PURPURA.**—This very rare condition is marked clinically by thrombocytopenic purpura, hemolytic anemia and varied neurological manifestations, and pathologically by widespread occlusion of small arteries and capillaries by hyaline plugs which are supposed to consist of platelets. In the involved arteries focal amorphous eosinophilic lesions replace the normal structure. These may be associated with aneurismal dilatation (Orbison).

**Secondary Purpura.**—So-called purpuric hemorrhages into the skin and mucous membranes may occur in a variety of pathological conditions. Toxic injury to the vessel walls may cause such hemorrhages in septicemia and in the infectious fevers, especially meningococcus meningitis, scarlet and typhus fevers, where they form a purpuric or hemorrhagic rash. Lesions of the bone-marrow with reduction in the number of blood platelets may cause purpuric manifestations more nearly related to those of primary thrombocytopenic purpura, though the platelets seldom fall to so low a level. Widespread secondary carcinoma of the marrow, lymphatic leukemia, and pernicious anemia may produce secondary purpura of this type, but the most striking example is aplastic anemia with its great reduction in the number of megakaryocytes from which the platelets are formed.

**The Exudative Diathesis.**—In some persons there is an increased permeability of the small blood vessels, as a result of which both plasma and red cells can pass out into the tissues. The platelets are normal. The condition is not permanent, but comes on in attacks resembling anaphylaxis. These cases are classed as *simple idiopathic purpura*, and are subdivided into a number of clinical groups. The escape of red cells from the vessels causes purpuric lesions, but the escape of plasma may cause urticaria in the skin and even more important visceral lesions. The following forms of the exudative diathesis may be distinguished:

**PURPURA SIMPLEX.**—A mild condition of purpura occurring in children. The hemorrhages are confined to the skin and clear up in a week or two.

**HENOCH'S PURPURA.**—In this form of the diathesis there are lesions in the skin, mucous membranes, and wall of the alimentary canal. Hemorrhage, urticaria, and erythema occur in the skin. There may be hemorrhage from the nose, stomach, bowel, and kidney. The most distinctive feature of this variety is the occurrence of transudation of serum into the wall of the stomach and intestine, thus causing pain, vomiting and diarrhea. Intussusception may occur. If the skin manifestations are absent

or delayed, the patient is in danger of having his abdomen opened and his appendix removed. The occurrence of fever and leucocytosis makes this danger even greater.

SCHÖNLEIN'S PURPURA.—This hardly deserves a special name. It is merely a form of the exudative diathesis in which the main manifestations are in the joints. The skin shows purpuric spots, urticaria, and erythema. There is a serous exudation into the joints causing an acute arthritis which is easily mistaken for rheumatic fever, especially as the temperature may be raised.

### HEMOPHILIA

Hemophilia, "the bleeding disease," is characterized by prolonged bleeding following a cut or trauma, but not by spontaneous hemorrhage. It is the most hereditary of all hereditary diseases, and repeats itself in generation after generation. Famous examples occurring in the royal families of Europe are known to everyone. It is almost invariably confined to males but transmitted by females of the family. It is, therefore, an example of sex-linked heredity. Birch finds that the urine of patients with hemophilia is deficient in the female sex hormone as tested by its effect in producing estrus in castrated female rats. Some workers have confirmed these results, but others have failed to do so. The hemorrhagic tendency appears in early childhood. A simple injury such as the extraction of a tooth may give rise to a fatal hemorrhage. Hemorrhage into the large joints after slight trauma is common. The hemophilic joint, usually the knee or elbow, develops a condition like chronic arthritis; some of the blood is not absorbed, and this causes proliferation of the synovial membrane and erosion of the cartilage.

The striking *blood change* is the very *prolonged coagulation-time*, sometimes several hours in length. The bleeding-time, *i. e.*, the time blood continues to flow from a minute puncture of the skin, is normal in the majority of cases, as there is no thrombocytopenia; it is the platelets which plug such a puncture. When the clot does form, it shows normal retraction. In these respects hemophilia differs from purpura hæmorrhagica, and also in the fact that spontaneous hemorrhage is the characteristic feature of the latter but not the former. The reason why blood continues to flow from a cut but not from the puncture made in estimating the bleeding-time is that hemorrhage from a cut is arrested primarily by the formation of a clot, whereas hemorrhage from a puncture is stopped by a plug of platelets.

No explanation of the disease is entirely satisfactory. It is believed now that the fundamental defect is in the plasma, involving the formation of thrombin from prothrombin, not, as formerly thought, a decreased fragility of the platelets. Thromboplastin is a substance which acts on prothrombin in the presence of calcium to form thrombin. In hemophilia the prothrombin is normal, but there is a congenital deficiency of plasma thromboplastin. The deficiency can be met by transfusions of plasma or whole blood.

### HYPERPLASTIC DISEASES

There is a group of diseases in which there is evidence in the blood of permanent hyperplasia of the hemopoietic tissues, with overproduction



of erythrocytes, granulocytes (myeloid cells), or lymphocytes. These conditions are known respectively as erythremia, myelogenous leukemia, and lymphatic leukemia. It seems probable that they are all neoplastic in nature.

**Leukemia.**—The essential feature of leukemia is a neoplastic proliferation of the leucoblastic tissues, as a result of which there is usually a great increase in the white cells of the blood. The increase may affect the myeloid cells (myelogenous leukemia), the lymphoid cells (lymphoid leukemia), or the monocytes (monocytic leukemia). Occasionally there is proliferation of white cells in the tissues, but they fail to appear in the blood stream. Such a condition is called *aleukemic leukemia*, but it would be much better to speak of aleukemic myelosis, aleukemic lymphadenosis, or aleukemic reticulo-endotheliosis, depending on which of the leucoblastic tissues is affected. It is not a separate disease entity, but merely a phase of the leukemic state, for sooner or later the blood becomes flooded with white cells. Even before this happens abnormal types of leucocytes may be found in the blood, although the total count is not raised. The leukemia is usually of the lymphatic type. It is evident that it may be difficult or impossible to draw any sharp distinction between aleukemic lymphadenosis and lymphosarcoma, for the latter condition may also terminate with a leukemic blood picture. There can be little doubt that from the pathological standpoint these conditions are closely related.

*Leukanemia* is another unsatisfactory term applied to a blood picture in which the features of leukemia and pernicious anemia are combined. The appearance is deceptive, for the case can always be shown to belong to one or the other group. In pernicious anemia primitive white cells may appear in the blood, and in leukemia megaloblasts may sometimes be found. *Leukanemia* is merely leukemia with severe anemia and the appearance of unusually primitive red cells in the blood.

The leukemias fall into three main groups, *myelogenous*, *lymphatic*, and *monocytic leukemias*. To these may be added a fourth, *acute leukemia*. Rare cases in which plasma cells are present in the blood and leucoblastic tissues in large numbers are known as *plasma cell leukemia*. The distinction between the fully developed and classical types is very easy. Sometimes the distinction is very difficult. The more acute the disease, the more difficult is it to be certain of the nature of the abnormal white cells, for it is the primitive blood cells which appear in the acute cases, and these lack distinguishing characteristics. It is customary to describe the different forms separately, but we shall consider them together in order to avoid needless repetition.

**THE BLOOD.**—In all forms of leukemia there is a marked increase in the number of the white cells. But such an increase is not of itself pathognomonic. Temporary counts as high as 100,000 may be met with in infective conditions, and as the result of treatment the white cell count may fall to normal in a leukemia. Much more characteristic is the presence of immature white cells, but these also may occur in other conditions which throw a strain on the bone-marrow, and a terminal leukemoid blood picture may closely simulate an acute terminal leukemia. At the same time it must be understood that in the great majority of cases the correct

diagnosis can be made without the slightest difficulty merely by a glance at the stained blood film.

In *myelogenous leukemia* there is a great increase in the granular series of cells, both primitive (myelocytic) and adult (polymorphonuclear) in type (Fig. 448); the cells in either of these groups may be neutrophil, eosinophil, or basophil. The myelocyte usually forms the prominent feature of the film (Plate XXVI, Fig. 1). It is a large cell about double the size of the polymorphonuclear, with an indented or lobed nucleus and abundant cytoplasm containing granules which may be fine and neutrophil, or coarse and eosinophil, or basophil. More primitive leucocytes are seen in the

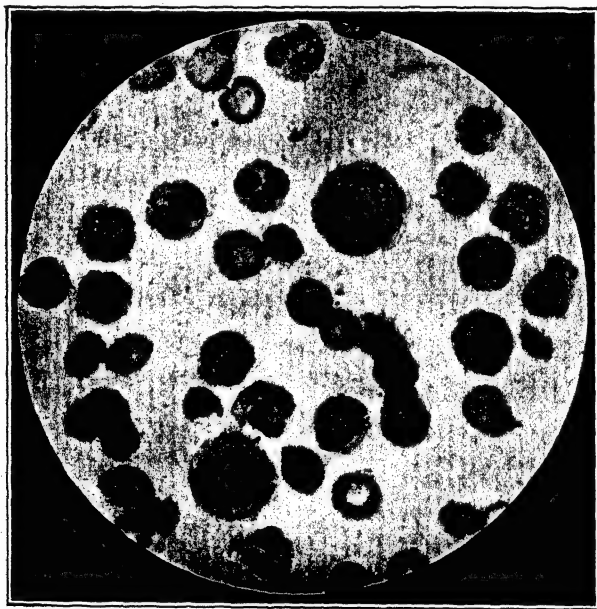
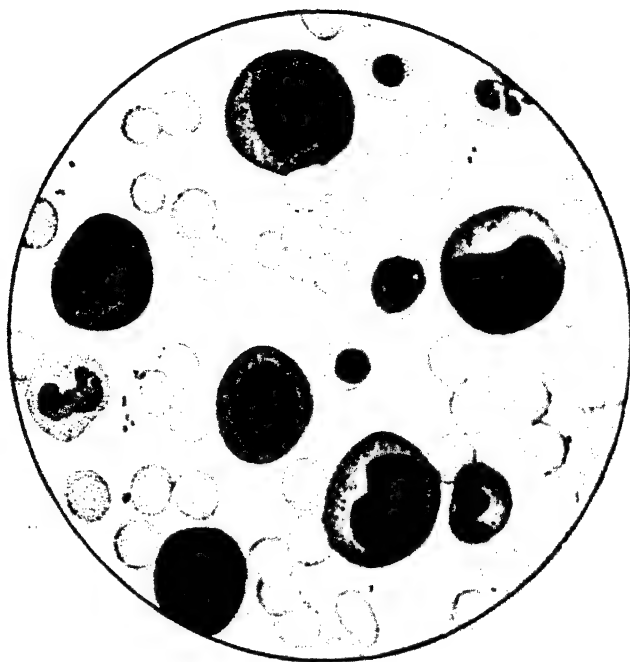


FIG. 448.—Myelogenous leukemia. Several myelocytes and very many polymorphonuclear leucocytes.  $\times 1000$ .

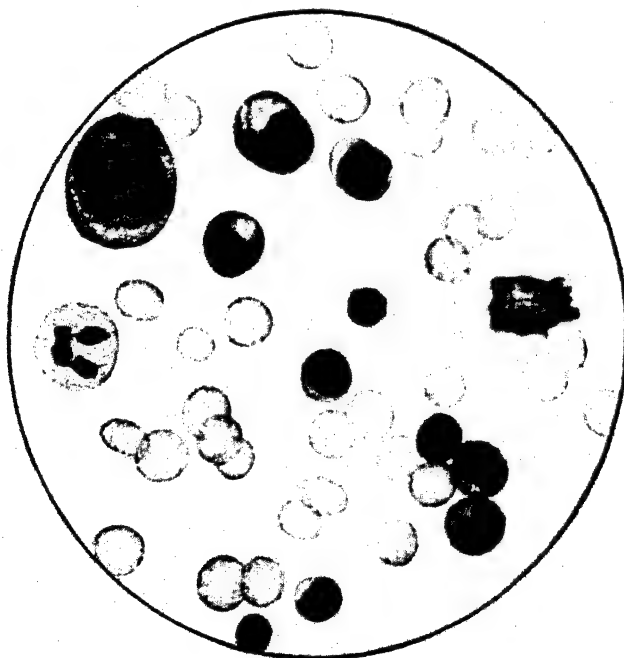
terminal stages or in the acute form of leukemia; these are myeloblasts with non-granular cytoplasm. The total leucocyte count averages 200,000, but it may go as high as 500,000 or even 1,000,000. As a result of radiation, benzol treatment or an acute infection such as pneumonia, there may be a great drop in the cell count, sometimes to normal. All the elements of myeloid tissue tend to take part in the abnormal activity; in other words, there may be a complete myelosis. Primitive red cells, therefore, appear in the blood, and normoblasts are more numerous than in any other disease—far more numerous than in pernicious anemia. Sometimes there are macrocytes and megaloblasts in considerable numbers. In spite of this activity in the bone-marrow there is a marked and progressive anemia, owing to the erythroblastic tissue being crowded out by the myeloid cells. In extreme cases there may be equal numbers of red and white cells. The

PLATE XXVI



**Fig. 1. Myelogenous Leukemia**

Myelocytes in various stages of development, an eosinophilic myelocyte, an eosinophil polymorphonuclears, normoblasts and platelets.



**Fig. 2. Lymphatic Leukemia**

Numerous small lymphocytes and one nuclear smudge, but no platelets.

megakaryocytes also take part in the myelosis, and there is, therefore, a great increase of platelets in the blood, sometimes to 2,000,000. The megakaryocytes themselves may be found in the blood. If it is remembered that there may be 1,000,000 white cells, 1,000,000 red cells, and 1,000,000 platelets, some of the principal features of the blood picture may be recalled. As the lymphocytes are not formed in the marrow, the percentage count is greatly reduced.

In *lymphatic leukemia* only the lymphoid cells are increased, and may form as much as 99 per cent of the total count, although 90 per cent is a commoner figure (Plate XXVI, Fig. 2). The average count is 50,000 to 100,000, rather lower than in the myelogenous form. The lymphocytes contain less cytoplasm than the normal small lymphocytes, so that they

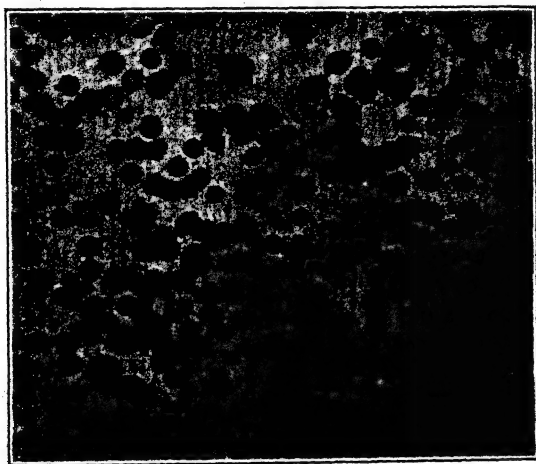


FIG. 449.—Lymphatic leukemia. Three types of cells can be seen: (1) small lymphocytes, (2) lymphocytic "smudges," (3) red blood cells.  $\times 400$ .

may appear as naked nuclei, and the cytoplasm usually contains no azurophil granules. Many of the lymphocytes appear to be dead, so that in the slide they look like a smeared nucleus, the so-called smudge (Fig. 449). Primitive myeloid cells may appear in the later stages, owing to irritation of the marrow produced by deposits of lymphoid cells. Secondary anemia becomes marked when the marrow replacement reaches a severe degree, but there is none of the erythroblastic activity characteristic of myelogenous leukemia, so that there are no normoblasts or only a very few. For the same reason blood platelets are much diminished in the later stages.

A consideration of the red cells and the platelets is of more use for differentiating myelogenous from lymphatic leukemia in difficult cases than is a study of the primitive white cells. Anemia is much more marked in the myelogenous than in the lymphatic form and megaloblasts are frequent. In lymphatic leukemia there is a great fall or complete disappearance of the platelets associated with bleeding, as indicated by petechiae in the skin and occult blood in the stool and stomach contents, whereas in the myelo-

genous form the platelets are not greatly affected until the late stages of the disease.

A rare *monocytic leukemia* has been described, in which there is supposed to be a large increase in the number of monocytes. It is probable that at least the majority of cases represent an atypical phase of myelogenous leukemia, because a large percentage have ended as the latter disease.

In *acute leukemia* the white cell count is seldom very high, and in the early stages it may be subleukemic (below 30,000) or aleukemic. At first sight nearly all the cells appear to be large lymphocytes (Plate XXVII), and it used to be thought that most cases of acute leukemia were of the lymphatic type. It now appears probable that the acute cases are mostly myeloid in type and that the predominant cells are myeloid stem cells. It is often impossible to distinguish with certainty between a myeloblast

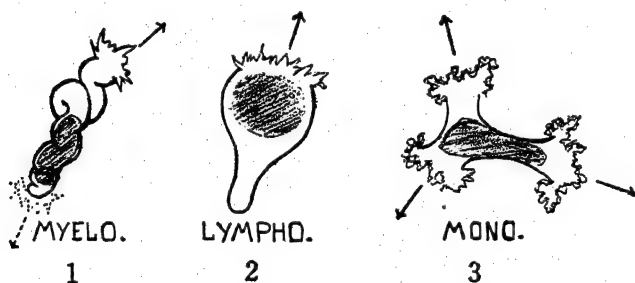
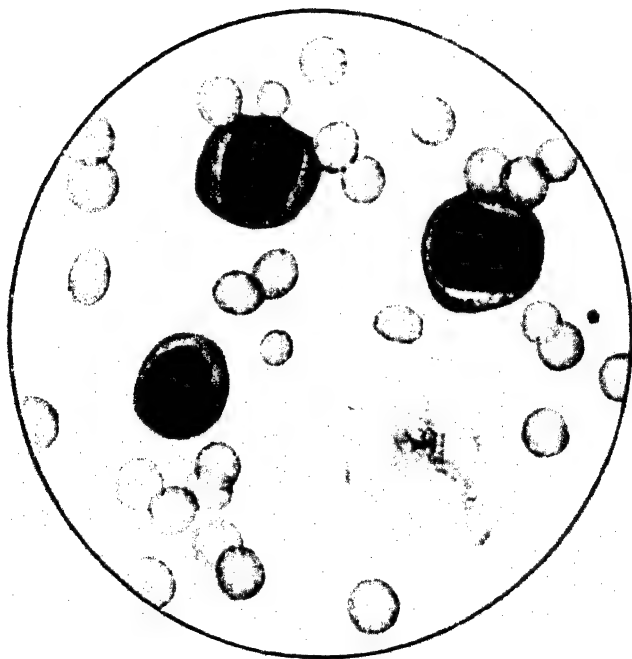


FIG. 450.—Myeloblast, lymphoblast and monocyte in motion. (Rich, Wintrobe and Lewis, courtesy of Bull. Johns Hopkins Hospital.)

and a lymphoblast, although the hematologists give a number of fine points of difference. The ordinary worker who is not a specialist in hematology will learn more by the indirect method of studying the more fully developed cells than by trying to stain stem cells by peroxidase or other special methods. If the primitive cells are myeloblasts, some myelocytes and a few polymorphonuclears will be noticed. If they are lymphoblasts the only differentiation is toward the lymphocyte. In such cases there may be very large lymphocytes with pale nuclei, the so-called Rieder's cells. When moving pictures of tissue cultures of stem cells are studied, striking differences at once become apparent, both in form and in method of locomotion (Rich, Wintrobe and Lewis). The myeloblasts become elongated and wriggle through the culture in a highly characteristic twisting, writhing, worm-like manner, whereas the lymphoblasts maintain a rather fixed shape like that of a hand mirror with a tail-like process, and move forward in a steady unperturbed manner, whilst monocytes continually throw out pseudopodia bordered by a broad, filmy, undulating, ruffle-like margin, and dart now in one direction, now in another (Fig. 450). Roentgen-ray therapy causes an initial drop in the white cell count; when it again goes up, the cells will be much more mature and readily recognized. There is severe anemia and great diminution of the platelets. Megaloblasts may be numerous, so that in the early aleukemic stage the disease may be mistaken for pernicious anemia.

## PLATE XXVII



### Acute Leukemia

Three blast cells and one nuclear smudge.

The most important feature in any form of leukemia is the presence of stem cells. These show that the case is definitely one of leukemia; the adult forms indicate the type of leukemia. Stem cells are recognized by their deeply basophilic cytoplasm, relatively large nucleus, and the nature of their nuclear pattern, the latter serving to distinguish them from adult lymphocytes. In the lymphocytes the nuclear chromatin forms a coarse pattern in heavy blocks, but no nucleoli can be distinguished. In contrast to this the nuclear chromatin of the stem cell is arranged in very fine strands like a sieve, and one or more nucleoli can usually be seen.

**BONE-MARROW.**—In *myelogenous leukemia*, as the name implies, the basis of the disease is a leucoblastic overactivity of the myeloid tissues. The red marrow becomes filled with immature white cells, and the fatty yellow marrow is converted into actively functioning tissue. Its gross appearance varies. It is firm, and may be gray, brown, or red; sometimes it is soft and purulent. The principal cell is the neutrophil myelocyte, but the microscopic picture is a complex one, for all varieties of leucocytes and of myelocytes are present. There are also groups of non-granular myeloblasts, and these cells may enter the blood in considerable numbers in the terminal stage of the disease. The megakaryocytes are increased in number, thus accounting for the rise in the platelet count. The erythroblastic tissue is largely replaced by leucoblastic elements. In *lymphatic leukemia* the marrow is invaded by lymphoid cells. At first there are only isolated islands of lymphoid tissue, but eventually the entire marrow, both red and white, is replaced by these cells. The gross appearance is the same as in the myelogenous form. In *acute leukemia* the marrow is packed with myeloblasts, together with a few myelocytes and a very few red cells; the erythroblastic tissue of the red marrow is almost entirely replaced.

**SPLEEN.**—In *myelogenous leukemia* the spleen is greatly enlarged and may fill the entire abdomen, sometimes weighing as much as 10,000 grams. It is dark in color, and infarcts are common, due probably to the formation of leucocytic thrombi in the small vessels. Microscopically the lymphoid tissue has disappeared, and the pulp has the same structure as the marrow, being crowded with myeloid cells of every description. It is probable that most of these cells have been arrested by the splenic filter, but there may possibly be some myeloid metaplasia, an assumption by the spleen of its primitive blood-forming function. In the *lymphatic form* the spleen is moderately enlarged, but in the very chronic cases the enlargement may be as great as in the myelogenous form. There is extreme hyperplasia of the lymph follicles, and the pulp is replaced by lymphocytes. In monocytic leukemia the spleen, lymph nodes, and liver are slightly enlarged and are full of monocytes. In the *acute form* the spleen is enlarged to a varying degree. The more acute the process, the less is the enlargement, and in the most severe and rapid cases it may hardly be enlarged at all.

**LYMPH NODES.**—In *lymphatic leukemia* the lymph nodes all over the body are enlarged. The greatest enlargement is seen in the abdominal glands which may be as large as walnuts. The normal structure is entirely replaced by lymphocytes, and the microscopic picture cannot be distinguished from that of a lymphosarcoma. The intestinal and other lymphoid tissue show the same enlargement. In the *myelogenous form* the

nodes are usually normal in size, although in exceptional cases they may be enlarged so as to suggest lymphatic leukemia. The sinuses are crowded with myeloid cells. In the *acute form* the lymph nodes and tonsils are enlarged and filled with myeloblasts.

**OTHER ORGANS.**—In the other organs the vessels are crowded with myelocytes or lymphocytes, depending on the form of the leukemia. Some of these cells appear to be outside the vessels, and there is often a suggestion of infiltration such as might occur in a neoplastic process. The *liver* may be moderately or markedly enlarged, and small nodules can be seen on the cut surface. Microscopically the arrangement of the cells is

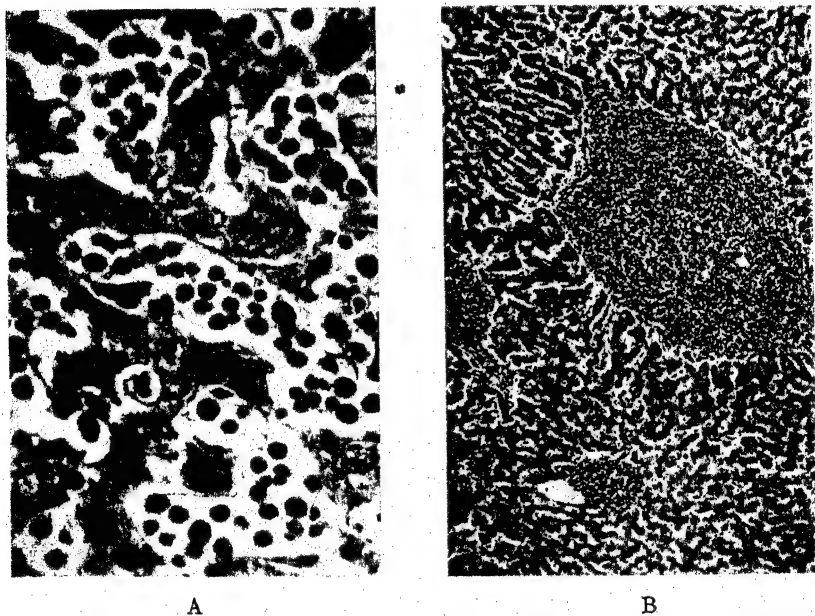


FIG. 451.—Liver in leukemia: (A) myelogenous, (B) lymphatic.

often strikingly different in the two types. In myelogenous leukemia the myelocytes distend the sinusoids to a marked degree, whereas in the lymphatic form the leukemic cells are for the most part gathered in large collections in the portal areas, although many are also seen in the sinusoids. In typical cases the distinction can be made at a glance at the liver sections (Fig. 451). The *kidneys* are pale and slightly or moderately enlarged. Here again the leukemic cells may lie outside as well as within the vessels. The heart, lungs, and other organs show a similar condition. *Hemorrhage* from the mucous membranes is a striking feature of acute leukemia, and in myelogenous leukemia there may be hemorrhage into the brain, the retina, and the middle ear.

In some cases there is marked infiltration and invasion not only of an organ but of the surrounding parts. This process, which has been called



*leukosarcoma*, is true malignant neoplasia. As a rule it develops at a single site.

**CHLOROMA.**—This very rare tumor is of theoretical interest, because it forms a link between leukemia and tumor growth; it is a malignant tumor with a leukemic blood picture. Green tumors (*kloros*, green) are formed in the flat bones of children and young adults, especially in the face and skull, where they may fill the orbit and push the eye forward. The sternum, spine, ribs and pelvic bones (red-marrow bones) are involved, and occasionally the long bones. There may be green tumors in the liver, kidneys, muscles and skin. The spleen and lymph nodes are often enlarged. The green color fades on exposure to air; the nature of the pigment is unknown. The bone-marrow of the long bones is filled with green tumor tissue. The tumors which can be detected clinically are under the periosteum, but it is probable that the primary growth is in the marrow, and that the periosteal tumors are secondary. The lesions consist of large non-granular cells similar to those of acute leukemia; there may be numerous granular myelocytes. The tissues (frozen sections) give the oxidase reaction. The tumors are much more invasive than the cellular collections of leukemia. The blood shows a picture of acute leukemia, although the total white cell count is not always increased. It used to be thought that the abnormal cells belonged to the lymphoid series, but it is now believed that they are myeloblasts. The distribution of the lesions in chloroma resembles that of multiple myeloma, the chief distinction between the two being that in myeloma the tumor cells do not enter the blood stream. Both are invariably fatal.

**THE NATURE OF LEUKEMIA.**—Leukemia is a disorderly, non-functioning proliferation of myeloid or lymphoid cells, and in this respect it resembles a malignant neoplasm. On the other hand it does not begin locally and spread by infiltration and metastases as does an ordinary cancer. When leukemic cells are injected into the anterior chamber of a rabbit's eye they do not multiply and invade as cancer cells do. In tissue culture malignant cells never differentiate into functioning cells, whereas leukemic cells may show functional activity such as phagocytosis and development into epithelioid cells in the presence of tubercle bacilli. It is very difficult to draw any sharp line between lymphatic leukemia and lymphosarcoma. Myelogenous leukemia, chloroma, and multiple myeloma have much in common, including the appearance of Bence-Jones' protein in the urine in all three conditions. No one denies that lymphosarcoma, chloroma, and myeloma are true tumors. It is true that in leukemia there is seldom any marked degree of infiltration, but we must remember that the leucocyte is a peculiar cell in a class by itself. As Gulland remarks: "It is the gypsy among cells. The body for its own purpose forms traps to hold it—marrow, lymph glands, and so on—and encourages it to proliferate there, but it is always eager to be off on its own business." We would not expect such a cell to be markedly infiltrative.

There seems to be no doubt that the leukemia which occurs in animals is a true malignant neoplasm with a marked hereditary tendency. It is not possible to be so dogmatic in man. Some authorities consider that it belongs to the dim borderland between inflammation and neoplasia. My own feeling is that leukemia is a form of neoplasm. The carcinogenic action of radiation is an accepted fact, and it is surely significant that leukemia is 9 times more prevalent in radiologists than in the general popu-

lation, and that in Japan those persons exposed to the atom bomb explosions developed the disease from 10 to 20 times as frequently as did those not exposed.

**THE RELATION OF SYMPTOMS TO LESIONS.**—The clinical manifestations of the three main forms of leukemia naturally differ considerably. The age incidence of acute leukemia is in early life, being commonest in the first five years; myelogenous leukemia usually occurs between the ages of twenty-five and forty-five years, and lymphatic leukemia between the ages of forty-five and sixty years. The patient suffers from the usual weakness, dyspnea and palpitation of severe anemia, due to replacement of the erythroblastic tissue in the bone-marrow. There may be a fullness and dragging sensation in the abdomen due to the great splenic enlargement. This enlargement may sometimes be as great in the lymphatic as in the myelogenous form. The condition of the superficial lymph nodes is not always a reliable indication as to the presence or absence of general lymphoid hyperplasia, for the deep nodes (abdominal and mediastinal) may be greatly enlarged though the superficial ones are barely palpable. Pain and tenderness of the sternum and more rarely of the long bones may be quite striking; this is caused by the hyperplastic-neoplastic process going on in the interior of the bone. Hemorrhages are common in all the varieties, particularly in the acute form, so that leukemia is classed as one of the "bleeding diseases." There may be hemorrhage from the nose, mouth, or bowel, or into the brain or retina. Bleeding gums and necrotic processes in the mouth, associated with fever and severe and progressive anemia are characteristic features of acute leukemia. The cause of the hemorrhage in leukemia is obscure. The coagulability of the blood is greatly decreased, but the reason for this is also unknown. Priapism may occur in the myelogenous form, due probably to engorgement of the penile cavernous tissue. Ascites, sometimes chylous, and chylous effusions in the chest may be due to pressure of enlarged glands on the thoracic duct. The basal metabolic rate is high owing probably to the increased metabolic activity of the great numbers of immature cells. The fever, which is most marked in acute leukemia, may be due to the same cause. A large amount of uric acid may appear in the urine owing to disintegration of nuclear material and liberation of nucleoproteins. The presence of Bence-Jones' protein in the urine is characteristic of bone-marrow lesions, being also found in chloroma and more particularly in multiple myeloma.

**Erythremia.**—This is a primary increase in the number of red blood cells, just as leukemia is a primary increase in the leucocytes. It is also known as polycythemia vera, polycythemia rubra, and Vaquez-Osler's disease. It must be distinguished from *erythrocytosis* or secondary polycythemia, a compensatory increase of red cells in conditions of insufficient oxygenation, *e. g.*, congenital heart disease, chronic valvular disease of the heart, emphysema, pulmonary arteriosclerosis, and residence at high altitudes. Erythrocytosis is a temporary condition, and corresponds to leucocytosis.

In true erythremia (polycythemia vera) there is an increase of the red cells irrespective of the needs of the body; they usually number from 7,000,000 to 10,000,000 per c.mm. In addition there is an increase in the volume of the blood, a true plethora, so that the total increase of red cells is greater than is indicated by the hemocytometer count. The blood becomes more viscid owing to the great number of red cells. The hemoglobin is increased to 125 or 150 per cent, and the color index is about 1. There is a moderate leucocytosis with a polymorphonuclear count of over 80 per cent. Oc-

casional primitive red and white cells (normoblasts and myelocytes) may be seen in the film. The bone-marrow is markedly hyperplastic, the change being chiefly erythroblastic (normoblastic) in type, but with areas of myelocytic reaction. It also shows capillary thickening and marked subintimal and adventitial fibrosis of the arterioles. Splenomegaly is present, usually moderate, but sometimes marked.

It has been shown experimentally that imbalance of the vasomotor mechanism may exert a marked influence on the peripheral blood cell mass (Schafer). Removal of the carotid sinus and the cardio-aortic proprioceptive nerves in dogs is followed by pronounced persistent polycythemia, the red cell count being restored to normal by paravertebral sympathectomy. The mechanism involved is probably the production of an anoxic condition of the bone-marrow due to vasoconstriction; this is known to stimulate the production of erythrocytes. These observations suggest at least a possible genesis of erythremia.

**THE RELATION OF SYMPTOMS TO LESIONS.**—The polycythemia appears to be due to a primary erythroblastic hyperplasia of the bone-marrow which may be neoplastic in character. A relationship to leukemia is suggested by the fact that occasional cases have changed from erythremia into leukemia of myelogenous type. A myeloblastosis in which the primary effect is on the erythroblastic tissue results in erythremia; when the primary effect is on leucoblastic tissue leukemia develops. The appearance of the patient is striking; the skin and mucous membrane of the mouth are red or bluish-red and the conjunctiva is blood-shot. The color is due to the increased number of red cells. At postmortem the visceral vessels are greatly distended owing to the increased blood volume; this is best seen in the mesenteric veins and these vessels may be thrombosed. Vertigo and sensations of fullness in the head are common; they are due to the great distention of the cerebral vessels, so that when the patient stoops he feels as if there was a rush of blood to the head. Hemorrhage from the mucous membranes or into the retina may occur on account of this vascular fullness. Peptic ulcer (usually duodenal) is a not uncommon complication. Possibly this is due to thrombosis of small vessels. The enlargement of the spleen may be regarded as a compensatory arrangement to deal with the increased number of red cells.

**Agranulocytosis.**—This condition is characterized by a remarkable disappearance of the granulocyte series of leucocytes from the blood and an accompanying drop in the total white cell count. It may not be possible to distinguish some cases from acute leukemia in the aleukemic stage. A differential point of value is that the platelet count is high in agranulocytosis but low in aleukemic leukemia. Most of the patients have been middle-aged women, and when accompanied, as is commonly the case, by necrotizing gangrenous lesions of the mouth involving the tonsils, gums, and even the bone of the jaw, it has in the past been nearly invariably fatal. The striking characteristic of the necrotic lesions of agranulocytosis is the almost entire absence of polymorphonuclears. There may be multiple ulcers of the stomach and intestine, and sometimes of the vulva. The association of leucopenia and destructive lesions of the mouth is known as agranulocytic angina. The condition is not a disease *sui generis*, but rather a symptom complex, an indication of the action of some powerful leucocidal poison, some destroyer of the bone-marrow, which may or may not be

accompanied by severe infection of the mouth. Three groups of cases may be distinguished: (1) A primary form with fever, ulcerative mouth lesions, and agranulocytosis, so that leucocytes are absent from the necrotic ulcers. No definite cause such as a constant and specific microorganism can be found. (2) Malignant leucopenia of bacterial origin, as in pneumonia, osteomyelitis, etc. (3) Malignant leucopenia of toxic origin; benzol, antisyphilitic arsenical preparations, and certain analgesic and antipyretic drugs such as amidopyrine and the barbiturate series, *i. e.*, chemicals containing the benzene ring, may so depress the bone-marrow that leucopenia results and bacterial infection of the mouth may develop in consequence. Should the patient continue to take the drug, as all too often happens, a fatal termination can hardly be avoided. Many of the patients display a hypersensitiveness to drugs, and probably this is a factor of great importance.

The *pathogenesis* of the second and third groups is easy to understand. That of the first group is much more obscure. It is known that certain pyogenic bacteria are capable of producing a leucocidin, a toxin specifically lethal for the leucocytes, the granular series in particular. *Staphylococcus aureus*, *Streptococcus hemolyticus*, and *Streptococcus viridans* are the most powerful members of this group. Dennis found that when these organisms, particularly *Streptococcus viridans*, were placed in celloidin capsules and inserted in the tissues, a diffusible toxin was produced which was powerfully leucocidal. When filtrates of the cultures in the capsules were mixed with leucocytes they caused disintegration of the polymorphonuclears, though the lymphocytes were unaffected. Pyogenic bacteria can produce agranulocytosis only when prevented from active penetration of the tissues, otherwise they merely excite leucocytosis. This suggests that some circumscribed focus of infection is present in the primary cases.

The *bone marrow* in the acute cases shows lack of maturation in the granular series of cells which therefore largely disappear, together with hyperplasia of the stem cells. The essence of the disease seems to be a maturation arrest affecting the granular leucocytes, so that they are unable to enter the circulation (poverty in the midst of plenty), a situation strictly comparable to that of pernicious anemia. In the more prolonged cases there may be hypoplasia of the myeloid tissue which contains large numbers of plasma cells and lymphocytes. In recovery there is a rapid change of stem cells into myelocytes and polymorphonuclears. In the neutropenia of overwhelming sepsis and arsphenamine poisoning there is not the same disappearance of adult granular cells from the marrow, and segmented forms can be seen.

**PRIMARY SPLENIC NEUTROPENIA.**—This condition, described by Wiseman and Doan in 1939, is characterized by marked neutropenia, splenomegaly and marrow hyperplasia. The white cell count may be extraordinarily low owing to disappearance of the neutrophils, in one case falling to 150 per c.mm. In a few hours after splenectomy the count may be increased 20 times. The condition is apparently a manifestation of hypersplenism, there being an accelerated destruction of the granular leucocytes by the reticulo-endothelial cells of the spleen. It is permanently cured by splenectomy. The spleen is rich in highly phagocytic cells containing polymorphonuclear leucocytes and erythrocytes. There is often a hemo-

lytic anemia and a diminution of platelets. The condition may therefore be compared to congenital hemolytic anemia and thrombocytopenic purpura, to which it is evidently related.

ADDITIONAL READING

- Agranulocytosis.** DARLING, *et al.*: *Am. J. Path.*, 1936, 12, 1. DENNIS: *J. Exper. Med.*, 1933, 57, 993. JAFFÉ: *Arch. Path.*, 1933, 16, 611.
- Anemia Due to Carcinomatosis.** WAUGH: *Am. J. Med. Sci.*, 1936, 191, 160.
- Anemia of Infection.** VAUGHAN AND SAIFI: *J. Path. and Bact.*, 1939, 49, 69. WINTROBE, *et al.*: *Science*, 1946, 103, 72.
- Aplastic Anemia.** RHOADS AND MILLER: *Arch. Path.*, 1938, 26, 648. THOMPSON, *et al.*: *Am. J. Med. Sci.*, 1934, 187, 77.
- Bone Marrow Development.** STEINBERG AND HUFFORD: *Arch. Path.*, 1947, 43, 117.
- Chloroma.** BRANNAN: *Bull. Johns Hopkins Hosp.*, 1926, 38, 189.
- Congenital Hemolytic Disease.** CAPPELL: *Brit. Med. J.*, 1946, 2, 601, 641. CRAIG: *Arch. Path.*, 1950, 49, 665. DARROW: *Arch. Path.*, 1938, 25, 378. DIAMOND *et al.*: *Pediatrics*, 1950, 6, 630. HSIA: *New England J. Med.*, 1952, 247, 668. JAVERT: *Surg., Gynec. and Obst.*, 1942, 74, 1. LEVINE, *et al.*: *Am. J. Obst. and Gynec.*, 1941, 42, 926. MACKLIN: *J. Pediat.*, 1944, 25, 533. POTTER: *Arch. Path.*, 1946, 41, 223.
- Erythroblastic Anemia.** CLIFFORD AND HERTIG: *New England J. Med.*, 1932, 207, 105. COOLEY: *Am. J. Dis. Child.*, 1927, 33, 786. WANSTROM: *Am. J. Path.*, 1933, 9, 623.
- Fibrosis in Hemolytic Anemia.** ELLIS *et al.*: *Am. J. Path.*, 1953, 29, 578.
- Folic Acid Deficiency Anemia.** ENDICOTT, *et al.*: *Arch. Path.*, 1945, 40, 364.
- Hemolytic Anemia.** DAMESHEK AND SCHWARTZ: *Medicine*, 1940, 19, 231. HADEN: *Am. J. Med. Sci.*, 1934, 188, 441; MANDELBAUM: *Ann. Int. Med.*, 1939, 13, 872. OWREN: *Blood*, 1948, 3, 231. RAPPAPORT: *Am. J. Path.*, 1953, 29, 590.
- Hemophilia.** HOWELL AND CEKADA: *Am. J. Physiol.*, 1926, 78, 500.
- Hypersplenism.** WISEMAN AND DOAN: *Ann. Int. Med.*, 1942, 16, 1097.
- Hypochromic Microcytic Anemia.** DAMESHEK: *J. A. M. A.*, 1933, 100, 540. MILLS: *Am. J. Med. Sci.*, 1931, 182, 554. WINTROBE AND BEEBE: *Medicine*, 1933, 12, 187.
- Leukemia.** FORKNER: *Leukemia and Allied Disorders*, New York, 1938.
- Life Span of Red Blood Cells.** CALLENDER, *et al.*: *J. Path. and Bact.*, 1945, 57, 129.
- Monocytic Leukemia.** DAMESHEK: *Arch. Int. Med.*, 1930, 46, 718. FOORD *et al.*: *J. A. M. A.*, 1933, 101, 1859.
- Pernicious Anemia.** CASTLE, *et al.*: *Am. J. Med. Sci.*, 1930, 180, 305. JACOBSON: *J. Path. and Bact.*, 1939, 49, 1. PEABODY: *Am. J. Path.*, 1926, 2, 487.
- Platelets.** OLEF: *Arch. Int. Med.*, 1936, 57, 1163.
- Polycythemia.** HARROP: *Medicine*, 1928, 7, 291. SCHAFER: *Ann. Surg.*, 1945, 122, 1098. WEBER: *Polycythemia, Erythrocytosis and Erythremia*, London, 1921.
- Primary Splenic Neutropenia.** WISEMAN AND DOAN: *Ann. Int. Med.*, 1942, 16, 1097.
- Purpura.** NICKERSON AND SUNDERLAND: *Am. J. Path.*, 1937, 13, 463.
- Purpura Hemorrhagica.** LIMARZI AND SCHLEICHER: *J. A. M. A.*, 1940, 114, 12.
- Pyridoxine Deficiency Anemia.** WINTROBE, *et al.*: *Bull. Johns Hopkins Hosp.*, 1943, 72, 1.
- Sickle-cell Anemia.** DIGGS: *South. Med. J.*, 1932, 25, 615. RICH: *Bull. Johns Hopkins Hosp.*, 1928, 43, 398. SYDENSTRICKER: *J. A. M. A.*, 1924, 83, 12.
- Stem Cells in Tissue Culture.** RICH, *et al.*: *Bull. Johns Hopkins Hosp.*, 1939, 65, 291.
- Stomach in Pernicious Anemia.** MAGNUS AND UNGLEY: *Lancet*, 1938, 1, 420. MEULENGRACHT: *Am. J. Med. Sci.*, 1939, 197, 201.
- Thrombocytopenia.** NICKERSON AND SUNDERLAND: *Am. J. Path.*, 1937, 13, 463.
- Thrombotic Thrombocytopenic Purpura.** ORBISON: *Am. J. Path.*, 1952, 28, 129.

## THE NERVOUS SYSTEM

## GENERAL PATHOLOGY OF THE NERVOUS SYSTEM

**DESCRIPTIVE OUTLINE.**—In describing so complex a structure as the brain, method is all-important. Consideration must be given to the following: meninges, cerebrum (cortex, white matter, basal ganglia, and ventricles), midbrain (including aqueduct, red nucleus and substantia nigra), pons and medulla (including fourth ventricle), cerebellum, base of brain, circle of Willis, and branches of the middle cerebral artery. The average weight in the male is 1400 grams, in the female 1250 grams. There is a minimal amount of cerebrospinal fluid in the subarachnoid space, much more in the basal cisterns. The pia-arachnoid is glistening, translucent, and is stripped off readily without tearing the brain (decortication). The subarachnoid space may be distended with fluid in conditions of edema. The convolutions are rounded and the sulci of moderate size. In cerebral atrophy the convolutions become shrunken and the sulci wide and deep, whereas in increased intracranial pressure the convolutions are flattened and the sulci obliterated. Not only the size but also the lining of the ventricles must be noted; it becomes granular in general paresis. The substantia nigra is examined for loss of pigment in chronic encephalitis lethargica. The vessels at the base should be soft and free from atheroma.

The *microscopic description* includes neurones, neuroglia, and vessels. The neurone consists of a nerve cell and fiber. In the nerve cell consider the nucleus, nucleolus, Nissl granules, pigment, and the shape and outline of the cell. In the nerve fiber consider the axis cylinder, medullary sheath, and sheath of Schwann. In connection with the neuroglia attention must be paid to astrocytes, oligodendroglia, and microglia. Finally, the perivascular (Virchow-Robin) spaces must not be forgotten, and the vessels which they surround.

**The Neurone.**—The central nervous system consists of two main elements: (1) the neurones and (2) the interstitial tissue or neuroglia. These react to irritants and injuries in entirely different ways. It is necessary to understand these reactions before the study of the special pathology of the nervous system can be undertaken. The neurone, the essential unit of the whole system, consists of a nerve cell and nerve fiber. The nerve fiber is made up of three constituents, the axis cylinder or axon, the medullary or myelin sheath, and the neurolemma or nucleated sheath of Schwann. Within the central nervous system the fibers consist only of the first two elements; the sheath of Schwann is added when the fiber becomes peripheral.

**WALLERIAN DEGENERATION.**—When a nerve fiber is divided or when the cell from which it arises is killed, the *distal part* of the fiber shows the characteristic changes first described by Waller in 1850. The axis cylinder becomes fibrillated and disintegrates, the medullary sheath breaks up into droplets of myelin which can be stained black by Marchi's method, and the

cells of the sheath of Schwann are converted into phagocytes which remove the remnants of the medullary sheath and axis cylinder. These cells also play an essential part in regeneration, a process which will be studied when the healing of nerve is considered. As the sheath of Schwann is not present in the central nervous system it is evident that healing after injury cannot occur in the brain and spinal cord. The complete process of Wallerian degeneration is best studied in a peripheral nerve, but the axonal and medullary sheath changes take place in the central nervous system also and have proved of extreme value in the experimental study of the path of fibers and tracts owing to the ease with which the degenerating myelin can be stained. The *proximal part* of the divided fiber also shows changes. The medullary sheath degenerates up to the first node of Ranvier, and the nuclei of the sheath of Schwann multiply in this segment of the nerve, and help to bridge the gap between the two ends of the divided fiber in a way which will be described in connection with injuries to nerves. The nerve cell from which the fiber arises undergoes Nissl's degeneration (see below).

Wallerian degeneration readily occurs as the result of *avitaminosis*, for the health of the medullary sheath is dependent on vitamins, especially B<sub>1</sub>. There is, however, no activity on the part of the Schwann cells. When vitamin B<sub>2</sub> is withheld experimentally degeneration of the anterolateral and dorsal tracts of the cord occurs as well as myelin degeneration of the peripheral nerves.

A word may be devoted to the *staining methods* used for demonstrating the medullary sheath changes in a degenerating nerve. Osmic acid stains myelin black, because the peroxide of osmium of which it is composed is reduced by the fat, forming a black compound with which it is insoluble in xylol, so that the method can be used for paraffin sections. The distinction between the normal and degenerating myelin is achieved by *Marchi's method*, which depends on the principle of selective oxidation. Normal myelin is readily oxidized but degenerating myelin very slowly oxidized when kept in an oxidizing fluid such as a solution of potassium bichromate. When the material is then treated with osmic acid, the normal tissue remains unstained as it has been fully oxidized and is therefore unable to reduce the osmic acid. The degenerated myelin, on the other hand, is very slightly oxidized, so that it readily reduces the osmium peroxide with the formation of the characteristic black compound. By means of Marchi's method, degenerating fibers can be traced through the length and breadth of the central nervous system, and the method has been of the greatest value in the experimental study of the course of nerve paths within that system. It is evident that too long a time must not elapse between the date of the injury and the application of the staining method, for if all the myelin has been removed there is no use trying to stain it. The Marchi method is used for the first few weeks after an injury. After that time the *Weigert myelin sheath stain* must be employed. This is the converse of the Marchi method, for it stains normal myelin dark blue or black; the degenerated fibers remain unstained, as their myelin has disappeared. The tissue is first mordanted in potassium bichromate so as to render the myelin insoluble, and is then stained with hematoxylin. The Marchi method is mainly used by the physiologist, who employs the experimental method. The Weigert method is of special value to the pathologist in the study of degenerative lesions of the white matter of long standing, *e.g.*, *tuben dorsalis*, disseminated sclerosis, etc.

**NISSL'S DEGENERATION.**—When a nerve cell is acted on by chemical or bacterial toxins it undergoes characteristic degenerative changes. Similar

changes are seen in a cell when the nerve fiber which arises from it is injured; this variety is known as axonal degeneration. The same secondary changes in the cell occur as the result of alcoholic and other forms of neuritis. The cell becomes swollen and rounded, the nucleus becomes eccentric in position and may be situated at the extreme margin, and the Nissl granules in the cytoplasm disintegrate and disappear (Fig. 452, A and B). It is this condition, known as chromatolysis, to which the degeneration owes its name. It is evident from what has been said that Nissl's degeneration is complementary to Wallerian degeneration. About three weeks after



FIG. 452A.—Normal nerve cell showing processes, concave borders, Nissl granules, nucleus and nucleolus.  $\times 600$ .



FIG. 452B.—Degenerated nerve cell: borders convex, loss of processes, Nissl granules and nucleus.  $\times 600$ .

division of the nerve, regeneration begins, the granules reappear, and the cell body is restored to normal. These regenerative changes are not seen in the cells of the upper motor neurones, just as no regeneration occurs in the fibers of these neurones.

The *distinction between upper and lower motor neurone lesions* is one of the most fundamental in neuropathology. Upper motor neurone lesions affect any part of the pyramidal tract from the motor cells in the cortex to the termination of the fibers around the anterior horn cells of the cord or the motor nuclei of the cranial nerves. Lower motor neurone lesions involve the anterior horn cells and their fibers or the motor nuclei of the cranial nerves and their fibers. Lesions of either the upper or lower neurone causes paralysis of muscles, but they can usually be readily distinguished from one another. The characteristics of *upper neurone lesions* are spasticity (increased muscle tone), exaggerated deep reflexes, and Babinski's sign (dorsiflexion of great toe on stimulation of sole of foot). *Lower motor*



*neurone lesions* are characterized by flaccidity of the paralyzed muscles, loss of the deep reflexes, muscular atrophy and severe trophic disturbances, fibrillary twitchings in the affected muscles, and the reaction of degeneration in these muscles. The commonest example of an upper motor neurone lesion is afforded by a hemorrhage into the internal capsule which destroys the pyramidal tract fibers. Examples of lower motor lesions are poliomyelitis (infantile paralysis), transverse myelitis, and the ordinary form of facial paralysis.

**PIGMENTARY CHANGES.**—In elderly persons and in degenerative conditions many nerve cells come to contain yellow pigment granules, probably a lipochrome. This must not be confused with the melanin which normally gives the cells of the substantia nigra a dark color.

**ATROPHY.**—There is marked general atrophy of the cerebral cortex in general paresis, Pick's convolitional atrophy and to a lesser degree in chronic alcoholism and senility. More localized atrophy may occur as the result of arteriosclerotic narrowing of the vessels. On account of the shrinkage of the brain there is widening of the subarachnoid space which is filled with fluid, and compensatory dilatation of the cerebral ventricles. In the atrophic areas the nerve cells are small and withered, and there may be an increase of yellow pigment in their cytoplasm.

**The Interstitial Tissue.**—The interstitial tissue of the central nervous system has long been known as the neuroglia. Glia means glue, and the neuroglia was regarded as a kind of putty which served the humble purpose of holding together the more noble neurones. In ordinary preparations the interstitial elements appear for the most part as naked nuclei. Gold and silver impregnation, however, gives an entirely different picture, and in place of naked nuclei we now see cells provided with a forest of fibers, which

present quite as striking an appearance as the cells and fibers of the neurones. By the aid of these methods, which we owe very largely to the Spanish school, it is possible to distinguish three elements in the interstitial tissue: these are the *astrocytes*, the *oligodendroglia*, and the *microglia*. The first two are ectodermal in origin, and together make up the neuroglia. The third is mesodermal in origin and is unrelated to the neuroglia.

**ASTROCYTES.**—The best known cells of the neuroglia are the astrocytes. The astrocyte is a large cell with numerous processes, at least one of which is attached to a small vessel by a curious expansion to which the names of vascular foot plate, suction apparatus, and sucker foot have been applied. The neurones are everywhere separated from the vessels by a layer of astrocytes. The astrocytes are best demonstrated by Cajal's gold-sublimate method (Fig. 453).

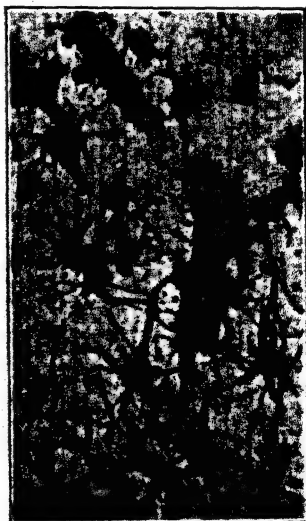


FIG. 453.—Gliosis (gold sublimate).  $\times 315$ .

The astrocyte plays an active part *in disease*. Hortega and Penfield have shown that the repair of wounds in the brain is due entirely to the activity of the astrocytes, which enlarge, multiply, and fill in the gap, just as fibroblasts do in other parts of the body. The gliosis seen in general paresis and other chronic inflammations consists of astrocytes and their fibers. In experimental intoxications the perivascular astrocytes develop into amoeboid cells, the processes and sucker feet being much swollen at

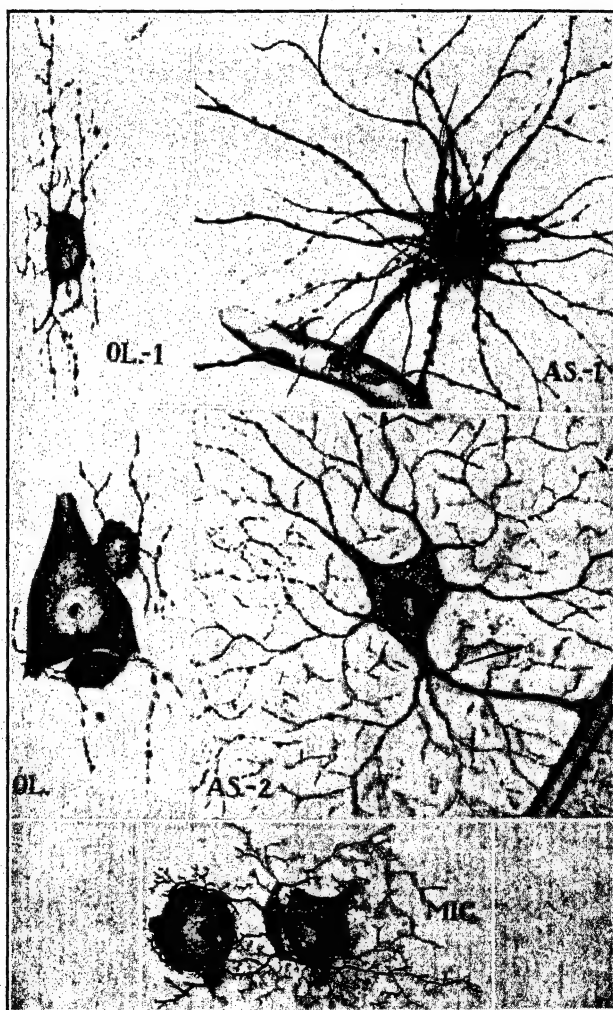


FIG. 454.—The interstitial cells of the central nervous system. AS-1, Fibrous astrocyte with several perivascular feet on blood vessel. AS-2, Protoplasmic astrocyte showing numerous processes but no fibrils. OL-1, Oligodendroglia. OL., Two oligodendroglia cells as perineuronal satellites around nerve cell in which nucleolus is distinctly shown. MIC., Microglia cells with numerous processes placed between and in contact with two nerve cells; in the latter the nucleolus can be distinguished. (Penfield, in Cowdry's Special Cytology, P. B. Hoeber, New York.)

first and later becoming absorbed into the body of the cell. Finally, the astrocyte is the cell from which the great majority of gliomas (astrocytomas, glioblastomas) arise. The oligodendroglia rarely and the microglia apparently never take on neoplastic growth.

**OLIGODENDROGLIA.**—This is the largest group of the interstitial cells, but the one about which the least is known. In ordinary sections they appear as naked nuclei arranged in rows between the nerve fibers in the white matter, and in the gray matter as satellites adhering to the nerve cells. When stained by Hortega's silver carbonate method the cells, which are much smaller than the astrocytes, are seen to possess a small number of fine processes (*oligos*, few) (Fig. 454). The *function* of these cells is obscure. They seem to bear the same relation to the myelin sheath of the nerve fibers in the central nervous system as the cells of the sheath of Schwann do in the peripheral nerves, so that they may have something to do with the preservation of the myelin. In *disease* they appear to play a part of no importance. They are evidently very sensitive to noxious agents, for they readily undergo acute swelling, becoming pale, vacuolated, and losing their processes. The cells are seldom seen in perfect form in human material, for they rapidly undergo autolysis after death.

**MICROGLIA.**—The microglia differs fundamentally from the other two elements in being mesodermal in origin, while they originate from ectoderm. The cells are very small (hence the name), and are provided with numerous fine branching processes which are stained by the silver carbonate method. Some of them form satellites to the nerve cells (Fig. 454). The microglia is not present at birth, but invades the brain from the pia in the course of a few weeks. These cells may be regarded as forming part of the reticulo-endothelial system, for when studied in tissue cultures by vital staining they behave in exactly the same way.

The *function* of the microglia is phagocytic; the cells are indeed the phagocytes of the central nervous system. Under pathological conditions they develop into the rod cells of general paresis and the scavenger cells (also known as compound granular corpuscles, fat granule cells and Gitterzellen) seen in brain softening. The transformation of the quiescent microglial cell into the amoeboid and phagocytic scavenger cell is a remarkable one. The cell body becomes swollen and rounded, the processes are thickened and then withdrawn into the cell, and the cytoplasm becomes filled with fat globules derived from the disintegrating myelin. The cells collect in enormous numbers at the site of injury, and then appear to carry the ingested myelin to the nearest vessels, into which they possibly discharge their content.

**CORPORA AMYLACEA.**—These are small spherical hyaline bodies, sometimes displaying a concentric structure, which are seen in large numbers in the nervous system in old age, and may occur earlier as a result of degenerative diseases. It used to be thought that they arose from the medullary sheath of degenerating nerves or possibly from nerve cells, but recent work seems to indicate that they represent degenerated microglial cells, or in some cases they may be formed from the oligodendroglia.

## INTRACRANIAL HEMORRHAGE

Hemorrhage in the interior of the skull may come from the brain or the meninges; it may be cerebral or meningeal. In traumatic cases the two may be combined.

**Cerebral Hemorrhage.**—Hemorrhage into the brain may be *traumatic* or *spontaneous*. It is important to remember that a patient who has had a trauma to the head may nevertheless be suffering from a spontaneous hemorrhage. The hemorrhage may come first, causing him to fall, injure his head, even fracture his skull. This is particularly true when the hemorrhage is in the internal capsule.

**TRAUMATIC HEMORRHAGE.**—Trauma may cause cerebral hemorrhage in two ways. (1) Hemorrhage is a more or less constant accompaniment of *laceration of the brain*. Fracture of the base or vault of the skull may be present, but it is important to realize that large cortical hemorrhage may occur without fracture. *Contrecoup* hemorrhage, which is situated on the side opposite the site of trauma, usually occurs without fracture; it is caused by the brain being thrown forcibly against the opposite side of the skull. A large hemorrhage due to trauma is very rarely (perhaps never) in the internal capsule, such hemorrhage being spontaneous. (2) *Multiple punctate hemorrhages* in the basal ganglia and elsewhere may be caused by trauma. These are probably the result of a wave of cerebrospinal fluid which the blow on the head causes to pass from the subarachnoid space into the perivascular prolongations of that space, with forcible stretching of the fibrillary extensions from the vessel wall to the perivascular sheath. Great numbers of small ring hemorrhages are formed around the vessels in this way, and if the patient survives these may be followed by gliosis which may form the organic basis of many of the post-traumatic neuroses. Martland has suggested that the condition known to prize-fighters as "punch-drunk" may be due to a wave of cerebrospinal fluid injuring the vessels; many old fighters develop corpus striatum symptoms (paralysis agitans, etc.).

**SPONTANEOUS HEMORRHAGE.**—This may take two very different forms, the *punctate* and the *massive*. The latter is the ordinary form of cerebral hemorrhage.

*Punctate hemorrhage* occurs as the result of infections and intoxications, as well as in the bleeding diseases. It may therefore be found in the infective fevers, septicemia, epidemic encephalitis, and bacterial endocarditis, in carbon monoxide poisoning and arsphenamine poisoning, and in pernicious anemia, leukemia, and purpura hæmorrhagica. In all of these conditions there is damage to the vessel wall. The hemorrhages are very small and very numerous. They are commoner in the white matter and basal ganglia than in the cortex. Each hemorrhage surrounds a small vessel, but often there is a narrow necrotic zone between the vessel and the hemorrhage, and there may be necrosis without hemorrhage. It would appear, therefore, that the necrosis is the primary condition and the hemorrhage secondary.

*Massive hemorrhage* constitutes what is commonly known as *apoplexy*. It usually occurs in middle-aged and elderly men with high blood pressure

and arterial degeneration. Hemorrhage may occur in the absence of hypertension. The opinion is gaining ground that apoplectic hemorrhage is not merely a question of a blood vessel bursting, as an aneurism of the aorta might burst. It takes place into soil which has been prepared by vascular thrombosis, occlusion, or perhaps even by spasm. As a result of the ischemia a focal encephalomalacia is produced, and it would appear that such softening is an essential precursor to rupture of a vessel (Fig. 455). An infected embolus lodging in one of the cerebral vessels may give rise to a mycotic aneurism, which on rupturing may cause a massive hemorrhage. So-called miliary aneurisms may be present. These are false aneurisms,



FIG. 455.—Hemorrhage in area of softening in distribution of right middle cerebral artery.

the blood having broken through a weak spot in the wall and produced a localized bulging of the adventitia; this may give way and be a source of hemorrhage. An occasional cause of hemorrhage is rupture of a congenital aneurism on the circle of Willis or one of its branches; this usually leads to subarachnoid hemorrhage, but the blood may make its way into the brain substance. Such an aneurism should be looked for in cerebral hemorrhage in a younger person.

In *hypertensive encephalopathy* three types of lesion may be encountered: (1) edema, causing such symptoms of increased intracranial pressure as headache, nausea, vomiting, dulness, etc.; (2) multiple miliary destructive lesions (ischemic), causing a wide variety of symptoms such as vertigo, transient hemiplegias and aphasias, convulsions, etc.; and (3) massive hemorrhage into larger areas of softening.

The common site of massive hemorrhage is the internal capsule and lenticular nucleus. The small arteries to the basal ganglia come directly off the middle cerebral, so that the pressure is not "stepped down" by continuous branching as in the case of the cortical branches. The lenticulostriate artery was long ago called "the artery of cerebral hemorrhage." The next most common site is the white matter of the frontal lobe, the hemorrhage coming from the anterior cerebral artery. Next come the pons and cerebellum. Hemorrhage into the pons may be due to unilateral increase of intracranial pressure, such as may be caused by a large hemorrhage into a hemisphere. The hippocampal uncus is herniated



Fig. 456.—Splinter hemorrhages in pons and midbrain.

through the opening in the tentorium, and the resulting pressure leads to pontine hemorrhage which may be the direct cause of death. The hemorrhage takes the form of small linear streaks, often termed splinter or crow's feet hemorrhages (Fig. 456). Spontaneous hemorrhage in the cerebral cortex is rare. Hemorrhage in the basal ganglia may extend inward, and more rarely outward. When it passes inward it may penetrate the caudate nucleus and rupture into the lateral ventricle (Fig. 457). About 40 per cent of fatal capsular hemorrhages rupture into the lateral ventricle before death. Pontine hemorrhages almost invariably rupture into the fourth ventricle. Spontaneous intracerebral hemorrhage only very rarely ruptures outward into the subarachnoid space.

The blood passes through the aqueduct and fills the entire ventricular system, passing thence to the subarachnoid space *via* the foramina in the roof of the fourth ventricle and filling the cisterns at the base of the brain. The original hemorrhage may be into the ventricles, usually from the anterior cerebral which supplies the tip of the caudate nucleus.

A clot is formed at the site of the hemorrhage, and this may be surrounded by petechial hemorrhages, caused probably by the sudden disturbance of pressure. The brain tissue in which the hemorrhage has occurred is torn up and completely disintegrated. The clot becomes softened and the destroyed brain substance liquefied, so that if the patient lives the hemorrhage is replaced by a cyst containing yellow or milky fluid. The surrounding tissue is stained yellow, and this discoloration may persist for a long time. *Microscopically* there is great destruction of neurones. The nerve cells are degenerated and the medullary sheaths are

broken up into droplets of myelin; presently the entire neurone disappears. In the case of the motor paths the degenerated fibers can be traced down through the brain stem (Fig. 458) into the cord. Two elements of the interstitial tissue, the astrocytes and the microglia, show marked activity. The *microglia* gives rise to large numbers of scavenger cells, which take up the myelin droplets and pigment granules, carrying them to the nearest vessels and perhaps discharging them into the lumen. The *neuroglia cells* (astrocytes) proliferate and form abundant fibers, so that a small cyst may be obliterated, while a larger cyst is shut off from the surrounding tissue by a glial zone. Granules of blood pigment indicate for many years the hemorrhagic origin of the cyst.

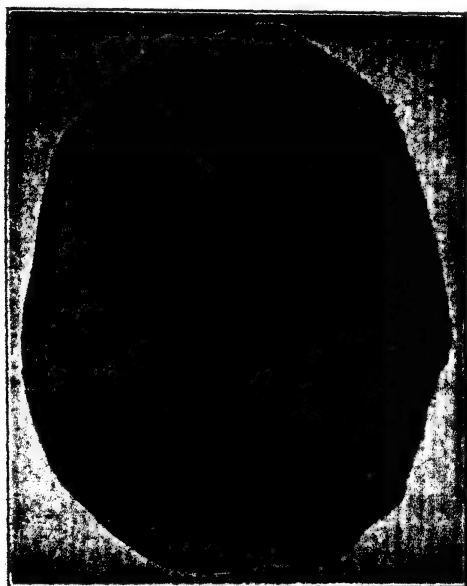


Fig. 457.—Cerebral hemorrhage. The hemorrhage has started in the internal capsule, passed inward through the optic thalamus, and ruptured into the lateral ventricle.

**THE RELATION OF SYMPTOMS TO LESIONS.**—Depending on the size of the hemorrhage, the patient with apoplexy either feels faint or loses consciousness. He may fall as though struck to the ground (*pleris*, to strike down), but sudden death is rarely due to cerebral hemorrhage unless it be into the ventricles or the medulla. The immediate loss of consciousness is due to the sudden cerebral anemia caused by compression of the capillaries by the hemorrhage, and the coma into which the patient may pass is to be attributed to the rapidly developing edema. It is the compression of the vital centers in the medulla by the edema which is the usual cause of death. The condition of the *cerebrospinal fluid* is of help in the diagnosis. In hemorrhage into the ventricles a large amount of blood is present in the fluid. When the hemorrhage does not communicate with the ventricles the fluid is at first normal, but in the course of three days it assumes a yellow tinge owing to blood pigment having seeped through into the ventricles. This is not found in any of the other comatose states which simulate cerebral hemorrhage.

The *focal lesions* depend on the site of the hemorrhage. When this is in the *internal capsule* there is paralysis of the face, arm, and leg of the opposite side. This paralysis, of course, is of the upper motor neurone type, with spasticity, exaggeration of the deep reflexes, Babinski's sign, etc., owing to removal of the cerebral influences which inhibit the normal tone of the lower motor neurone. At first, however, there is flaccidity with loss of deep reflexes instead of spasticity, owing to shock produced by the hemorrhage. The motor fibers occupy the anterior two-thirds of the posterior limb of the capsule, while the sensory fibers pass up in the posterior limb, so that if the hemorrhage extends sufficiently far back there will also be hemianesthesia of the paralyzed side. Just behind the capsule pass the fibers of the optic radiation, and if this is involved there will be homonymous hemianopia

(blindness in one-half of the field of vision). *Hemorrhage into the ventricles* is characterized by sudden loss of consciousness, loss of all the reflexes, and a rapid rise of temperature; the condition soon proves fatal. In *pontine hemorrhage* hyperpyrexia is again present, and the pupils are extremely contracted (pin-point pupils) owing to interruption of the pupil-dilating fibers. Hemiplegia will be present if the pyramidal tract is involved. *Cerebellar hemorrhage* is accompanied by persistent vomiting, nystagmus and deviation of the eyes to the side of the lesion, and a tendency to fall to that side. As the pyramidal tract is not involved there is no paralysis.



FIG. 458.—Hemiplegia: degeneration of right crossed and left direct pyramidal tract.

**Meningeal Hemorrhage.**—Meningeal hemorrhage may be *extradural*, *subdural*, or *subarachnoid*.

1. **EXTRADURAL HEMORRHAGE.**—This is commonly called *middle meningeal hemorrhage*, being due to injury to the middle meningeal artery from fracture of the lower part of the parietal bone or the squamous portion of the temporal bone. It is caused by a direct blow; the elastic recoil of the skull separates the dura from the bone, and the spaces become filled with blood. A large clot is formed outside the dura over the vertex and this presses on the brain (Fig. 459). Prompt operation with ligation of the bleeding vessel is needed, otherwise the patient will die from compression of the brain. The *clinical picture* is highly characteristic. There may be brief loss of consciousness owing to the blow. This is followed by a *lucid interval* of some hours, at the end of which time symptoms of compression appear owing to the gradual accumulation of blood between the skull and the brain. There is no blood in the cerebrospinal fluid. A useful localizing sign is a fixed dilated pupil on the *same side* as the lesion, due probably to herniation of the hippocampal uncus with pressure on the third nerve as it crosses the greater wing of the sphenoid. There may also be conjugate deviation of the eyes to the opposite side due to irritation of the oculomotor center in the second frontal convolution.



2. SUBDURAL HEMORRHAGE.—Subdural hemorrhage (Plate XXVIII) may be regarded as venous, just as extradural hemorrhage is arterial in origin. The condition, which is at least 4 times as common as extradural hemorrhage, is of great importance, because the life of the patient depends on a correct diagnosis and this is easily missed. It is customary to recognize a traumatic and a spontaneous form, but it is becoming doubtful if the latter is more than a myth, for the traumatic factor in the etiology is often slight and easily overlooked. The cause is a blow in the frontal or occipital region (*e. g.*, knocking the head against a shelf or door), which injures the cerebral veins passing into the sagittal sinus. As there are no septa to localize the extravasated blood, it may spread from the frontal to the

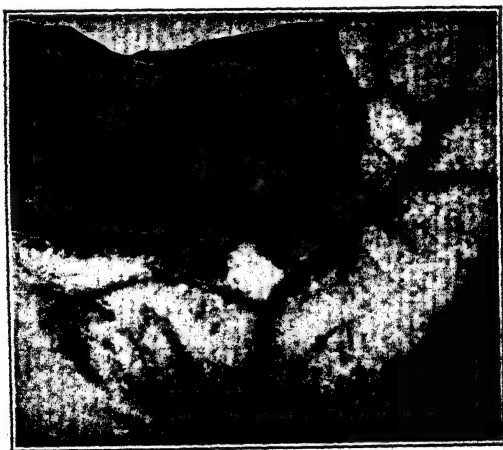


FIG. 459.—Extradural hemorrhage.

occipital pole and from the sagittal sinus to the Sylvian fissure. The symptoms may not come on for weeks or even months after the injury. This is explained by the unique subsequent behavior of the clot. This is not absorbed as it would be in other serous sacs, for the subdural space is closed and without lymphatics. The clot becomes liquefied and surrounded by a mesothelial membrane, so that a cyst is formed which separates the dura from the brain. Into this cyst cerebrospinal fluid is drawn by the osmotic pressure of the blood, so that the tension in the cyst continually increases, with corresponding pressure on the brain. At the site of a subdural hematoma, therefore, the dura is lined by a dirty-green, gelatinous membrane which is easily detached, and the cyst contains dark green, thin fluid under pressure. *Pachymeningitis hemorrhagica interna* is a term which has long been applied to the supposedly spontaneous form in which a membrane containing great numbers of large blood spaces is found on the inner surface of the dura. Hemorrhage is supposed to occur at intervals from these giant capillaries, but they are also present in traumatic cases.

The *symptoms* are mental confusion and somnolence coming on weeks or even months after some trivial trauma to the head. Temporal tenderness is a valuable sign. Most of the cases are men over forty years with lessened elasticity of the skull and more fragile cerebral veins. Rather remarkably, the spinal pressure is not increased, but the fluid may be yellow (xanthochromia) due to histiocytes traversing the arachnoid barrier and giving up their blood pigment to the cerebrospinal fluid in the subarachnoid space. As might be expected, surgical treatment is highly satisfactory.

*Intracranial hemorrhage of the newborn* is a variety of subdural hemorrhage. It is a common cause of death in the newborn. The child is cyanosed, the respirations difficult, the pulse slow, the fontanelle bulging, and there may be twitching movements. Death may occur in a few hours or in the course of a day or two. If the child survives, paralytic and mental symptoms may develop later. The hemorrhage is due to tears in the tentorium cerebelli or the falx cerebri or to injury to the cerebral veins passing from the cortex across the subdural space into the superior longitudinal sinus. These injuries are produced by the severe molding of the head which occurs at birth, and not necessarily by the use of instruments. The hemorrhage is largely supratentorial and often bilateral. It is commoner in the premature than in the full-term infant owing to immaturity of the fibers of the dural septa. The arachnoid is often torn, so that blood is found in the cerebrospinal fluid. Lumbar puncture is of great use in doubtful cases. The gravity of the condition depends not merely on the extent of the lesion, but on whether the child suffers from a hemorrhagic diathesis which interferes with the clotting of the blood. This is due to a low prothrombin content of the blood, and the condition can be treated by injections of vitamin K, or prevented by giving the vitamin to the mother before delivery.

3. SUBARACHNOID HEMORRHAGE.—This may be traumatic or spontaneous. (1) *Traumatic hemorrhage* is likely to occur in all lacerations of the brain, so that blood will appear in the spinal fluid. The presence of blood in the subarachnoid space may irritate the cells of the arachnoid and cause blockage of the arachnoid villi through which the cerebrospinal fluid is absorbed into the venous blood sinuses. As the fluid cannot escape in the normal way it may collect in pools and cause pressure atrophy of the underlying cortex. It is possible that this may partly explain the puzzling post-traumatic neuroses and psychoses. The presence of pressure atrophy can be demonstrated in the living patient by means of encephalography or injection of air into the subarachnoid space.

(2) *Spontaneous subarachnoid hemorrhage* is a fairly common condition. The blood may leak into the subarachnoid space from a cerebral hemorrhage, or the subarachnoid hemorrhage may be primary. The common lesion found is atheroma of the cerebral vessels or the arteries at the base of the brain. This may or may not be associated with a ruptured congenital aneurism on the circle of Willis (Fig. 460), or on one of its branches such as the anterior or middle cerebral. The little aneurism (berry aneurism) is covered by blood clot and is easily missed unless specially looked for. Sometimes the blood may pass into the brain, giving a picture easily mistaken for that of ordinary cerebral hemorrhage. The condition, which should

## PLATE XXVIII



### Subdural Hemorrhage

In addition to the blood clot on the brain and the inner surface of the dura there is diffuse staining of the cerebrum.

always be considered in intracranial hemorrhage in a young person, is described more fully in connection with intracranial aneurisms. These aneurismal cases are usually fatal. There is another group of cases which usually recover and are probably due to some rather mild infection, some meningo-encephalitis, which especially attacks the vessels. They occur in groups or little epidemics, a fact which serves to strengthen the idea that they are infections, although of this there is no direct proof.

The *symptoms* are characteristic. The very sudden onset of severe headache and stiffness of the neck may suggest meningitis. Milder cases are mistaken for epidemic encephalitis. In the aneurism cases there may be partial recovery after the initial onset, only to be followed a few days later by a second more violent and often fatal attack. There is apparently at first a partial break with some leakage and the formation of a false aneurism, followed later by complete rupture into the subarachnoid space. The cerebrospinal fluid contains a large amount of blood, which can be distinguished from accidental blood due to the puncture, by the fact that there is some hemolysis with yellow coloration (xanthochromia) of the fluid after centrifugation. Both albuminuria (often massive) and glycosuria are frequent.

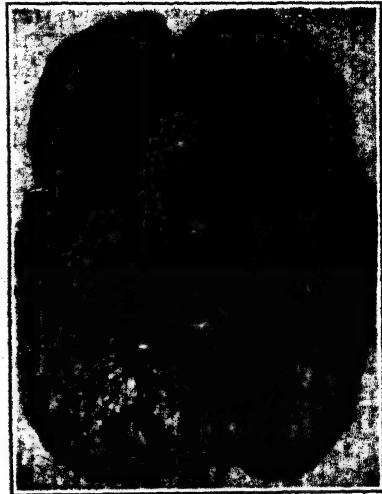


FIG. 460.—Congenital aneurism of circle of Willis with hemorrhage.

## VASCULAR LESIONS

**Arterial Obstruction.**—A cerebral artery may be obstructed partially or completely. *Partial obstruction* may be due to atheroma, obliterative arteriosclerosis, or syphilitic endarteritis. The resulting anoxia may lead to degeneration of the sensitive neurones and proliferation of the more resistant neuroglia. Such gliosis is seen in old age, and is most marked in senile dementia. The alternation of minute foci of cystic softening and glial scars may give the cortical surface a granulated appearance.

If attention is focussed on atheromatous patches in the larger arteries at the base of the brain it will often happen that there is no apparent relationship between the clinical picture and the vascular lesions. This is not true if the smaller vessels within the brain substance are examined. Here the characteristic lesion is a peculiar change which has been called obliterative arteriosclerosis (Scheinker). Its distinguishing feature is extreme thickening of the intima due to cellular (fibroblastic) proliferation

and hyperplasia of the ground substance with corresponding narrowing of the lumen. Later the cells may degenerate and be replaced by a network of connective tissue fibers. The lesion can be distinguished from the hyperplastic arteriosclerosis of hypertension in that in the latter the media and adventitia are thickened as well as the intima and there is an absence of intimal cellular proliferation.

*Complete obstruction* is due to embolism or thrombosis. (1) *Cerebral embolism* usually affects the middle cerebral artery on the left side, due probably to the more direct origin of the left carotid artery from the aorta. The clot which forms the embolus may arise in any of the usual sites (vegetation on mitral or aortic valve, thrombus in left auricular appendix or on an atheromatous ulcer of the aorta, etc.). If the clot is septic, an abscess or a mycotic aneurism may be formed, and the latter may rupture with fatal results. Usually it is aseptic, and the result is cerebral softening. Cone and Barrera have shown that when an aseptic infarct is produced in a dog the area and the overlying meninges become flooded with polymorphonuclears in eight hours with a maximum at forty-eight hours. The leucocytes may reach the cerebrospinal fluid in small or large numbers by the perivascular spaces or by direct invasion of the subarachnoid space or ventricles. The process, which is comparable to the leucocytosis in infarction of the myocardium, may be mistaken clinically for abscess or meningitis owing to the pus cells in the spinal fluid. The area of softening depends partly on the site of the obstruction and partly on the collateral circulation. If, as is usually the case, the middle cerebral is blocked before the branches to the basal ganglia are given off, both that region and the cortical area are deprived of blood and may undergo softening. There is a good collateral circulation in the cortex, so that the softening is often confined to the basal ganglia, but if the vessels are narrowed by arteriosclerosis or if the heart's action is weak, the collateral circulation is insufficient and the cortex may suffer severely. The motor fibers passing down through the internal capsule are destroyed, so that the opposite half of the body is paralyzed. If the obstruction is above the point where the arteries to the basal ganglia are given off, the lesion will be entirely cortical. (2) *Thrombosis* is usually due to atheroma or syphilis of the artery; atheroma is the common cause after middle life, and syphilis at an earlier age. The arteries most often the seat of thrombosis are the middle cerebral, posterior cerebral, and basilar. Thrombosis of the basilar artery causes softening of the pons. The symptoms develop more slowly than in embolism, but the effect is the same.

So far the discussion has concerned only the intracranial arteries. It is common knowledge that it is the exception rather than the rule to find a satisfactory explanation in these vessels for cerebral infarction, softening and hemorrhage. Yet as Hicks and Warren remark: "Among the most common misconceptions are those still widely taught that infarcts of the brain are usually caused by thrombosis and that most cerebral hemorrhages result from rupture of sclerotic arteries." The cause of the ischemia and the source of many cerebral emboli is often to be found in the internal carotid artery. Miller Fisher points out that the cervical portion of this artery, the main vessel of supply of blood to the brain, lies in a no-man's

land between general pathology and neuropathology, so that its examination at autopsy has been largely neglected. Fisher found complete or almost complete occlusion of one or both of the internal carotids in eight per cent of routine autopsies, the incidence being greatest between sixty-five and eighty years of age. The occlusion is due to atherosclerosis, which is most marked in the carotid sinus (Fig. 461). Thrombosis is a frequent accompaniment, and the thrombus may give rise to otherwise unexplained emboli.

These vitally important facts are not new. In 1905 Chiari found thrombi on atheromatous plaques in the carotid sinus in seven cases in 400 consecutive autopsies, some of which were the source of cerebral emboli. Hultquist in 1942 studied the entire carotid system in 1400 autopsies and wrote a monograph on the subject. The carotid sinus proves to be a site prone to atheroma second only to the abdominal aorta. Carotid artery arteriography has shown many cases of occlusion in the living patient (Moniz).

Fisher emphasizes the fact that internal carotid occlusion seems to be a frequent cause of single and double hemiplegia and may be associated with the picture of senile dementia. Moreover, hemiplegia occurring as a result of the shock of myocardial infarction, severe hemorrhage and major surgery may be determined by unsuspected carotid artery blockage. As in the case of the coronary arteries the occlusion may be silent owing to an adequate collateral circulation. These observations on the relation of occlusion

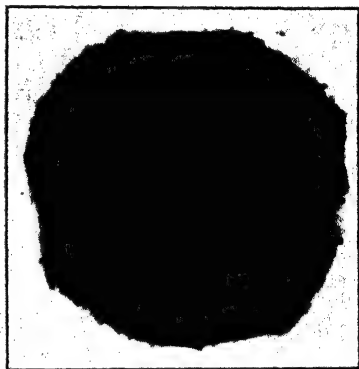


FIG. 461.—Occlusion of internal carotid artery at site of sinus. (Kindness of Dr. C. Miller Fisher.)

of the internal carotid artery to cerebral lesions of ischemic and hemorrhagic nature may serve to displace many of the fanciful explanations such as vasomotor spasm offered in the past for such cases where no adequate cause can be found within the cranium.

**CEREBRAL SOFTENING.**—When an area of the brain (or spinal cord) is deprived of its blood supply it undergoes necrosis and in the course of a few days becomes liquefied and converted into a creamy material (Fig. 462). In the experimental animal temporary arrest of the circulation for five minutes causes necrosis and softening of the cerebral cortex; if the arrest is maintained for over seven minutes there is complete destruction and liquefaction of the brain substance (Weinberger *et al.*). The color is usually pale, but in the course of time becomes yellow owing to blood pigment and the lipid liberated from breaking down myelin. In exceptional cases it is red on account of marked congestion. The sequence of events is similar to that which occurs in hemorrhage. As liquefaction proceeds a cyst is formed with clear or milky contents and a yellow margin. The neuroglia proliferates and forms a limiting zone around the cavity.

(Fig. 463.) When the cortex is involved a cyst is formed beneath the meninges, or there may simply be atrophy of the convolutions with depression of the affected area.

The *microscopic changes* involve both the neurones and the interstitial tissue. A smear of the liquefied material shows at first granules and globules of lipid, the remains of cells and fibers, and large numbers of scavenger cells. In sections of the affected area there is complete necrosis and loss of all structure. Secondary (Wallerian) degeneration can be traced down

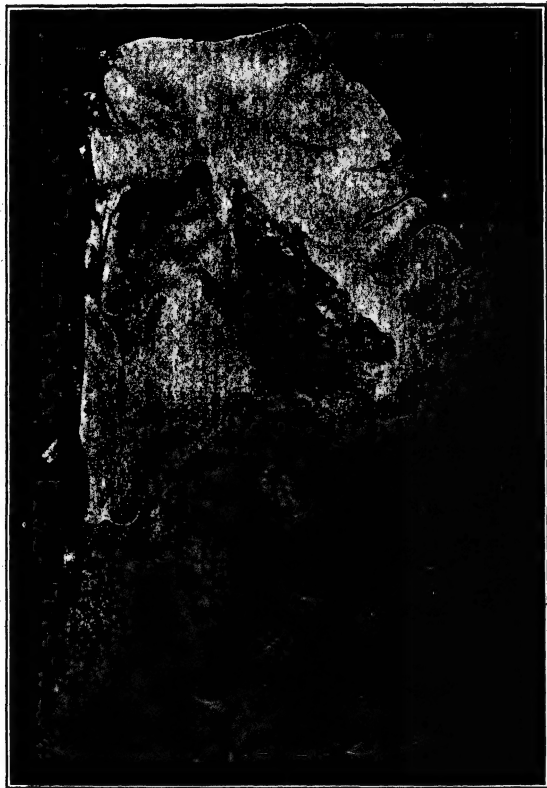


FIG. 462.—Large area of softening in the lenticular nucleus with cyst formation, due to vascular occlusion.

the course of the motor fibers through pons, medulla, and cord, the droplets of myelin being demonstrated by the Marchi method. At a later date Weigert's myelin sheath stain shows complete disappearance of the fibers, whose place is occupied by proliferated neuroglia. A zone of gliosis is seen around the wall of the cyst. But the most characteristic feature of a recent softening is the presence of enormous numbers of large pale scavenger cells derived from the microglia and filled with lipid globules taken up from the disintegrating myelin (Fig. 464). These cells are known by a variety of names such as compound granular corpuscles, fat granule cells, Gitter-

zellen (lattice cells), and Hortega cells on account of the demonstration by del Rio Hortega that they are microglial in origin. Frozen sections stained for fat with Scharlach show in a beautiful manner the lipid character of the cell contents. The walls of the vessels are infiltrated with these cells, which seem to be discharging their contents into the lumen.

**Venous Obstruction.**—This is caused by thrombosis of the venous sinuses. Not infrequently the cerebral thrombosis is part of a general venous thrombosis. In other cases it is of local infective origin, as in sinus thrombophlebitis due to spread of infection from the middle ear, nose, etc.

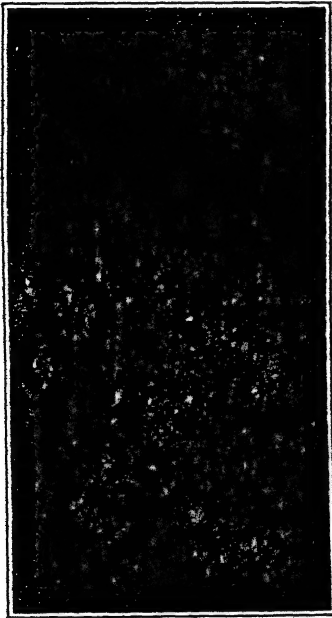


FIG. 463.—Gliosis at margin of softened area.  $\times 300$ .

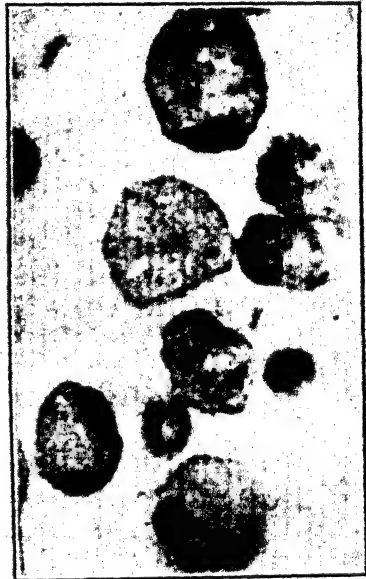


FIG. 464.—Scavenger cells of the brain (Hortega cells) filled with lipid. These cells are derived from the microglia.  $\times 1000$ .

The superior longitudinal sinus is most often affected. In severe cases there may be a remarkable dilatation of the superficial veins which become completely thrombosed, so that the surface of the brain seems to be covered with dark worms.

**Intracranial Aneurisms.**—These aneurisms are nearly always extra-cerebral, for they are situated on the circle of Willis or its main branches. Aneurismal dilatations in the brain substance are seldom true aneurisms. There are three main types of intracranial aneurisms. In their order of frequency these are the *congenital*, the *mycotic*, and the *arteriosclerotic*. Aneurisms due to syphilis are practically non-existent.

1. **CONGENITAL ANEURISM.**—These aneurisms, which may be multiple, firm small swellings on the vessels of the circle of Willis, the middle



cerebral, anterior cerebral, and anterior communicating (Fig. 460). These are commonly known as berry or miliary aneurisms. Although often present in young persons, the usual age period is between 40 and 60 years. The most striking peculiarity of the aneurism is that in every case it is situated at the bifurcation of the vessel. At this point there is often an absence of the muscular tissue of the middle coat in normal persons, which may be looked on as a congenital vascular malformation or defect. The same localized medial defect is found in the congenital aneurism, the wall of which is formed by greatly thickened intima, with complete absence of media and internal elastic lamina. There may be other vascular anomalies, *e. g.*, coarctation of the aorta. Glynn does not believe that there is any proof that congenital medial defects are the cause of the aneurisms, for he finds such defects as common among controls as in cases of aneurism (80 per cent in each group). He points out that in the vessels of the circle of Willis all the elastic fibers are concentrated in the internal elastic lamina, not distributed throughout the media and adventitia as in other arteries. For this reason a patch of atheroma may destroy all the elastic tissue and thus produce an aneurism. Atheroma is almost constantly present in these aneurisms, but has been regarded as secondary rather than primary. If this interpretation is correct, berry aneurisms must be regarded as atheromatous, not congenital, in origin. Carmichael has suggested that in most cases of atheroma the commonly associated fibrohyaline thickening of the wall compensates for the destruction of the elastica. Whatever the truth may be it would seem that the term berry aneurism is to be preferred to congenital aneurism as a description of the arterial lesion. Rupture of the aneurism leads to hemorrhage into the subarachnoid space which is usually fatal. If the aneurism is on the anterior cerebral or the anterior communicating artery and therefore wedged in between the frontal lobes, it may rupture into the brain substance. The same is true of the middle cerebral. These cases are easily mistaken in the autopsy room for ordinary cerebral hemorrhage, the aneurism being lost in the hemorrhage and readily overlooked.

2. MYCOTIC ANEURISM.—An infected embolus, usually from a vegetation on a heart valve, lodges in the middle or anterior cerebral artery and sets up an acute arteritis. This weakens the wall so much that a small mycotic aneurism is formed, which is certain to rupture unless the patient dies before that happens.

3. ATHEROMATOUS ANEURISM.—This form usually occurs over the age of fifty years. If, however, the so-called congenital aneurisms are admitted to be of atheromatous origin, the lesion is common between the ages of twenty and thirty.

## DISTURBANCES OF CEREBROSPINAL FLUID CIRCULATION

**Hydrocephalus.**—Hydrocephalus or water on the brain is a condition in which the cerebrospinal fluid collects inside (and sometimes outside) the ventricles, so that these cavities become greatly dilated with an accompanying pressure atrophy of the cerebral tissue. The cerebrospinal fluid is secreted by the choroid plexus of the lateral and other ventricles,

passes along the aqueduct of Sylvius to the fourth ventricle and escapes through the foramina in the roof of that ventricle to enter the basal cisterns of the subarachnoid space. From there it flows upward through the narrows between the brain stem and the incisura in the tentorium, to expand again into the shallow lake of the cerebral portion of the subarachnoid space. It also passes down from the basal cisterns into the spinal canal, where it can be withdrawn by lumbar puncture. The normal pressure is 7 to 9 mm. of mercury or 110 to 130 mm. of water. The fluid is absorbed into the large venous sinuses, especially the superior longitudinal sinus, by way of the arachnoid villi, which are diverticula of the subarachnoid space that project into the lumen of the sinuses. The Pacchionian bodies are hypertrophied villi which are only found in adult life. It is evident that if the fluid is unable to escape from the ventricles absorption is impossible, if it cannot pass from the basal cisterns to the cortical subarachnoid space absorption will be impaired, and there may be local interference with absorption if the arachnoid villi and Pacchionian bodies are blocked. The obstruction may occur at three points: (1) in the aqueduct, (2) in the roof of the fourth ventricle, and (3) around the mesencephalon where it passes through the narrow opening in the tentorium. The first two cause *internal hydrocephalus*, the third causes *communicating hydrocephalus*, the ventricles being in open communication with the basal cisterns and the spinal canal. All three are obstructing.

The ordinary hydrocephalus of children is due to obstruction either in the roof of the fourth ventricle or in the aqueduct. The exact cause of the obstruction is not certain. As Dorothy Russell remarks, quoting Spiller: "It is not necessary to study the different works on hydrocephalus very exhaustively to find that actually observed lesions are much rarer than theories explanatory of the causes of hydrocephalus." It is probable that adhesions due to a mild meningitis are the most frequent cause of obstruction in the roof of the ventricle. The aqueduct may be occluded by a delicate veil-like membrane which is probably the result of a developmental defect, but may in some cases be due to slight intra-uterine inflammation. Congenital hydrocephalus is due to obstruction of the aqueduct. A rare cause is the so-called *Arnold-Chiari malformation*, a congenital deformity of the hind-brain in which the brain stem is displaced through the foramen magnum, plugging of which prevents absorption of the cerebrospinal fluid. Hydrocephalus may complicate meningitis or brain tumors. Tuberculous meningitis, the lesions of which are essentially basilar, is always accompanied by dilatation of the ventricles, due to the formation of a plastic exudate on the roof of the fourth ventricle with blockage of the foramina of Magendie and Luschka. Various lesions of the arachnoid villi and Pacchionian bodies may prevent absorption and cause the fluid to accumulate over the cortex in the subarachnoid space (Winkelman and Fay). The fluid may be dammed back in the ventricles; indeed a marked degree of hydrocephalus can be produced experimentally by injecting lamp-black into the basal cisterns and in this way blocking the villi. Aplasia of the villi may cause congenital hydrocephalus. Blocking of the villi by exudate occurs in acute and tuberculous meningitis and as the result of hemorrhage into the subarachnoid space. It is therefore

advisable to remove as much blood as possible by lumbar puncture. Hydrocephalus is a common accompaniment of brain tumors and is the chief cause of such classical symptoms as headache, vomiting, and optic neuritis. It may be produced in a variety of ways. (1) A glioma of the fourth ventricle or mid-brain may cause complete obstruction of the aqueduct. (2) A tumor above the tentorium may press the cerebrum down so as to wedge the brain stem into the opening in the tentorium, thus producing obstruction to the flow of fluid from the basal cisterns to the cortical subarachnoid space and so preventing absorption. (3) If the brain is pressed upward



FIG. 465.—Hydrocephalus. The ventricles are moderately dilated.

against the vault of the skull the subarachnoid space will be obliterated and again absorption will be interfered with. It is small wonder, then, that hydrocephalus is a common accompaniment of brain tumor.

The greatest degree of hydrocephalus is seen in young children, in whom the head is still capable of enlargement. The enlargement may be enormous, with wide separation of the cranial bones, islands of bone in a sea of membrane. The little wizened face is surmounted by the huge dome-like cranium, which toward the end becomes little more than a bag of jelly. The degree of dilatation of the ventricles varies from the slightest to the most extreme (Fig. 465). In the latter the cerebral tissue is reduced to a mere shell from pressure atrophy, but the subtentorial structures remain wonderfully intact. This is one of the saddest features of the disease, for the mental deterioration may be complete, yet the intact vital centers

in the medulla allow the child to continue its miserable and vegetative existence.

**Cerebral Edema.**—Edema of the brain is a condition in which fluid collects in the brain substance, particularly in the perivascular and perineuronal spaces. This must be sharply distinguished from accumulation of fluid in the subarachnoid space. The two conditions may be associated, but the mechanism by which they are produced is quite different. The edema may be due to general or local causes. *General causes* such as cardiac or renal edema may cause cerebral edema. In nephritis and particularly in uremia the edema may be marked. Chronic alcoholism is often associated with a "wet brain." *Local causes* are hemorrhage, inflammation, and tumor of the brain. Any such focus is sufficient to disturb the intracranial circulation sufficiently to allow fluid to pass from the vessels into the soft tissues of the brain. The edematous brain is pale, moist, and softer than normal. The distinction between gray and white matter is not well marked. The convolutions are swollen and the sulci narrowed. Moisture exudes from the cut surface. When the edema is due to general causes there is likely to be an excess of fluid in the subarachnoid space. When the cause is local this space may be empty owing to pressure of the brain from below.

**TRAUMATIC EDEMA.**—The edema which follows trauma is of extreme practical importance on account of the disturbance which it causes in the circulation of the cerebrospinal fluid. The best example of this type of edema is seen in fracture of the skull. It is not the injury to the bone which is of importance but the laceration of the brain, as a result of which local edema and swelling rapidly develop. If the swelling is marked and persistent the brain tends to be pushed up or down, depending on the site of the hemorrhage. If it is pushed up against the skull, the subarachnoid space over the vertex is obliterated so that no absorption of fluid can occur. If it is pushed down, the opening in the tentorium is plugged so that the fluid cannot pass from the basal cisterns to the upper subarachnoid space. In both cases the result is the same—a great accumulation of fluid at the base of the brain with increasing pressure on the vital centers in the medulla, as indicated by slowing of the pulse and respiration. This clinical picture of compression is usually attributed to "medullary edema," but it is evident that the effects are not due to a local edema of the medulla but to disturbance of the cerebrospinal fluid circulation.

**Epilepsy.**—Epilepsy may be either idiopathic or secondary to some cause, obvious or doubtful as the case may be. In the so-called *idiopathic* category one of the largest groups is that characterized by temporal lobe seizures (dreamy states, feeling of unreality, unpleasant odors). Penfield and his associates have drawn attention to the presence of temporal lobe lesions in these cases, ischemic in nature and apparently due to pressure on vessels at the time of birth. In 157 cases of temporal lobe seizures this type of lesion was present in 100, the remaining 57 cases showing evidence of post-natal injury, intracranial infection or neoplasm in the temporal region (Earle, Baldwin and Penfield). The seizures may begin in childhood or may be delayed to the second or third decade. In one-quarter of the cases there was a history of difficult birth. The gross lesions are sclerotic areas in-

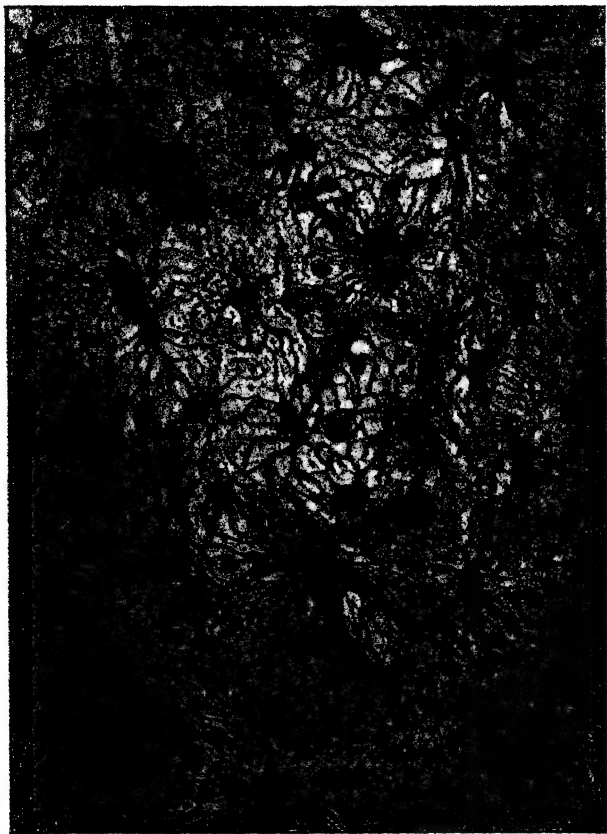
volving a single gyrus or it may be the entire lobe. These areas are tough, yellow, avascular and shrunken. Microscopically there is a striking increase in the astrocytes, sometimes giving the appearance of an astrocytoma. There may or may not be a focal loss of nerve cells and fibers. The hippocampus and uncus are supplied principally by the anterior choroidal artery, which at birth is as large as the middle cerebral. This and other vessels have to cross the sharp edge of the tentorium against which they may be compressed. It is common knowledge that in the adult increased intracranial pressure can cause hippocampal and uncal herniation through the incisura tentorii. Penfield has shown that the same can happen in the newborn if labor is prolonged, with resulting ischemia and eventual sclerosis, a condition to which he has given the name of *incisural sclerosis*.

The *secondary* cases are due to such gross lesions of the brain as tumor, abscess, etc. In post-traumatic *epilepsy* the pia-arachnoid is thickened, and localized collections of fluid with atrophy of the corresponding convolutions can be seen on the operating table, although not in the post-mortem room. It is possible that the initial lesion is an arachnoiditis, the effect of which is to block the villi and to divide the subarachnoid space into areas in which the excess of fluid is confined.

## INJURIES OF THE BRAIN AND SPINAL CORD

**Laceration.**—Varying degrees of laceration are common results of head injury. This may occur with or without fracture of the skull. Fracture, indeed, seems to act as a safety valve for the brain, as in a case which I observed of a child who fell on his head from a height of two stories and sustained a fracture of the skull which extended from the base over the vertex to the base on the other side, but suffered no permanent ill effects. Often the laceration is most marked on the side opposite to that on which the blow is struck, the condition known as *contrecoup*. Contrecoup injury, which is commonly seen on the under surface of the frontal lobes and the temporal and occipital poles, may be more or less severe than the lesion at the site of the original injury. Occasionally the only hemorrhage found is in the pons or mid-brain due to impact of the brain stem against the basi-occiput. When the patient dies months or years later, cortical defects may be seen at the summits of the convolutions. The end result is a worm-eaten scarred area of cortex to which are attached the overlying arachnoid and dura. There is demyelination and neuroglial scarring of the underlying white matter. These lesions, often small and easily overlooked, may be yellowish-brown in color due to the presence of old blood pigment. The acutely injured brain is swollen, a swelling usually attributed to edema, although some workers question this explanation. Petechial hemorrhages are common. Under the microscope they take the form of so-called ring hemorrhages, a ring of red blood cells around a central necrotic area. The lesions are really in the nature of hemorrhagic infarcts rather than true hemorrhages; blockage of a small vessel leads to necrosis, with diapedesis of red cells into the necrotic zone.

## PLATE XXIX



Proliferation of astrocytes as the result of injury to the brain. The astrocytes are attached to the walls of the bloodvessels by long processes. Stained with gold chloride.

The *neuroglial reaction* to trauma has attracted much attention, both in the experimental animal and in man. All three glial elements, microglia, oligodendroglia and astrocytes, share in the changes. The *microglia* reacts to local destruction and disintegration of tissue. Transition forms of microglia are found within a few hours of laceration, but fully formed compound granular corpuscles, the scavenger cells of the central nervous system, only appear after three or four days; they remain as long as products of disintegration are present. The *oligodendroglia* reacts immediately after injury with enlargement and vacuolization of the cells; in a few hours there is acute swelling which persists for weeks, especially about the local injury. Acute swelling of the oligodendroglia is one of the commonest and least specific of glial reactions. It is found in every patient dying in coma. The *astrocytes* undergo regressive changes with the development of amoeboid forms in the first few days after injury. In the zone nearest the injury there is complete destruction, but beyond this zone there is active proliferation, with cellular mitosis and the formation of a dense feltwork of fibrils. (Plate XXIX.) This gliosis persists indefinitely in the neighborhood of the lesion. The damaged part of the brain shrinks, and fluid collects in the subarachnoid space. A vascular woof of sclerotic tissue is formed which is adherent above to the meninges and below to the general vaso-astral framework of the brain (Penfield). The scar undergoes contraction over a period of months and years, exerting a constant pull not only locally but on the whole framework of the brain. This is probably one of the most important causes of *traumatic epilepsy* of the Jacksonian type, which may come on a number of years after the original injury. If the injured tissue can be removed soon after the trauma, formation of the vascular connective tissue is prevented, and the likelihood of subsequent epilepsy greatly diminished.

**Concussion.**—This is a transient state following head injury, of instantaneous onset, with purely paralytic symptoms, no sign of cerebral damage, and always followed by amnesia for the actual moment of the accident. As the result of a blow on the head, which as a rule does not produce a fracture, the patient instantaneously loses consciousness, and at the same time passes into a condition of profound shock. The face is pale and the body covered with a cold sweat, the temperature is subnormal, the pulse imperceptible, and the respiration almost suspended. The patient soon recovers consciousness, and as reaction sets in the temperature rises and the pulse becomes bounding. In some cases an unpleasant sequel is a marked degree of irritability, a condition of "cerebral irritation" which may last for a long time.

If a patient suffering from concussion should die, the autopsy findings are inconclusive. There may be laceration of the brain especially on the under surface of the frontal and temporal lobes, with hemorrhage into the subarachnoid space. These lesions can have nothing to do with the sudden loss of consciousness and development of shock. Petechial hemorrhages may be scattered through the brain, owing probably to a wave of cerebrospinal fluid which the blow causes to travel from the subarachnoid space into the perivascular sheaths and the perineuronal spaces. The sudden anemia produced by this perivascular wave in the cerebral cortex would

account for the loss of consciousness, while a similar condition in the medulla would produce the phenomena of shock. As the vessels become filled again the stage of reaction would set in. The subsequent irritability is probably due to injury produced by the sudden violent distention of the perivascular sheaths, of which the petechial hemorrhages are the visible indication, and this may be followed by gliosis. The allied subject of "punch-drunk" has already been discussed in connection with traumatic cerebral hemorrhage.

**Compression. Increased Intracranial Pressure.**—The brain is confined within a rigid bony box and contains the most sensitive cells in the body. An increase of pressure is therefore of great importance, and may give rise to the clinical picture known as compression. The four chief causes of compression are hemorrhage, abscess, tumor, and edema. Edema may complicate any of the other three, and is the cause of compression (in conjunction with hydrocephalus) in laceration of the brain and fracture of the skull. At the site of the pressure the vessels are emptied of blood, and it is the medullary ischemia thus produced which renders the condition so dangerous. The fluid is driven out of the cerebral subarachnoid space into the spinal canal, thus giving the brain a little more elbow-room, but the relief is only temporary. The dura is tense and the convolutions flattened so that the sulci can hardly be detected. In the traumatic cases where the brain is forced up against the skull, the subarachnoid space may be empty when the dura is incised. In general cerebral edema and in cases where the cerebrospinal fluid eliminating mechanism is blocked (arachnoid villi and Pacchionian bodies) there may be an abundance of fluid over the cortex.

**SYMPTOMS.**—The symptoms of compression are the same no matter what the original cause may be. The higher centers suffer first, so that the mind is dulled and the patient gradually sinks into coma. Pressure on the motor centers may first cause convulsive movements, followed later by paralysis. The vital centers in the medulla are first stimulated and then depressed, so that the pulse, respirations, and blood pressure are all affected. It is not too much to say that with the exception of motor paralysis nearly all the really important symptoms of intracranial lesions are due to increase of the intracranial pressure. This is particularly true of brain tumor. The classical symptoms of that condition—headache, vomiting, and optic neuritis—are late manifestations of increased pressure. Nearly all the surgeon's troubles in the operating room are due to this cause, and every effort must be made to combat the increase. Particularly in traumatic cases, repeated lumbar puncture and dehydration of the brain by the intravenous use of hypertonic salt solution or the administration of magnesium sulphate are of much greater value in reducing the pressure than a decompression operation.

**Spinal Cord Injuries.**—The spinal cord is most frequently injured by fracture or dislocation of the vertebræ. Hemorrhage, wounds, etc., are much less common causes. At the site of the lesion there is the same disintegration, softening, and liquefaction as occurs in the brain. The immediate result of a severe injury is motor and sensory paralysis below the lesion and loss of the organic reflexes. If the lesion involves the cervical enlargement, the upper limbs will show a lower motor neurone type of paralysis owing to destruction of the anterior horn cells, while the lower



limbs will show an upper motor neurone paralysis from destruction of the pyramidal tracts. It is extremely interesting to examine sections taken above and below the lesion and stained with Weigert's myelin sheath stain. If sufficient time has elapsed for degeneration of the medullary sheaths to occur, all the motor tracts *below* the lesion will be degenerated while the sensory tracts are intact, but *above* the lesion the motor tracts are intact while the sensory ones are degenerated.

*Hematomyelia* or hemorrhage into the cord is nearly always due to trauma. There is first softening of the cord, followed later by hemorrhage. The hemorrhage may extend longitudinally in the gray matter of the cord, sometimes involving the greater part of the cord. In the rare cases which recover the blood may be replaced by glial tissue, giving a lesion very similar to syringomyelia.

### INTRACRANIAL SUPPURATION

Suppuration within the cranial cavity may take the form of *extradural abscess*, *abscess of the brain*, and *sinus thrombophlebitis*. Acute meningitis is also a suppurative condition, but is more conveniently considered under a separate heading.

**Extradural Abscess.**—The infection spreads from the skull as the result of osteomyelitis of the cranium, a compound fracture, middle-ear disease, or frontal sinus infection. A collection of pus is formed external to the dura, and as that membrane offers a stout barrier to the spread of infection, the abscess may remain localized for a considerable time. The scalp over the inflamed area of bone becomes swollen and edematous, forming what is known as *Pott's puffy tumor*, a condition described by Percival Pott in 1760.

**Abscess of the Brain.**—The infection may spread from a local focus or may be carried from a distance by the blood stream. The common *local focus* is middle-ear suppuration. It may also result from infection of the frontal and nasal sinuses, from osteomyelitis of the skull, or from a compound fracture. Infection from the middle ear may spread up through the tegmen tympani, in which case the surface of the bone is eroded, or by the veins, when no external lesion can be seen either on the bone or the cerebral surface. *Distant infection* most often comes from a septic focus in the lung, usually bronchiectasis; sometimes there is empyema. It is probable that infection spreads from the lung to the brain by the vertebral system of veins. This would explain the fact that there are no abscesses in other organs. The abscess is often single, the common site being the white matter of the frontal lobe (Fig. 466).

The abscess cavity is filled with pus in which there may be staphylococci, streptococci, or pneumococci. *Bacillus pyocyaneus* is often present, giving the pus a greenish color. The common site in middle-ear cases is the temporo-sphenoidal lobe, sometimes the cerebellum. The latter is much the more serious because of the frequency of meningitis, probably due to the depth of the cerebellar folia. When the infection comes from the frontal and nasal sinuses the frontal lobe is involved. A well-formed capsule is produced at the end of three weeks by fibroblasts in the adventitia of ves-

sels. It is only after the formation of this capsule that an operation can be undertaken with hope of success. The best results are those obtained in abscess secondary to middle-ear infection, the worst in cases secondary to lung abscess. It is remarkable how silent a brain abscess may be for a considerable time, especially if it is in the temporo-sphenoidal lobe. The temperature may be normal, the pulse is slow (abnormally so), and there may be very little leucocytosis. The cerebrospinal fluid is usually normal, apart from increased pressure, but if the abscess approaches the surface polymorphonuclears may appear in the fluid, due to seepage of toxic material quiescent for many months, but eventually it will rupture into a ventricle or reach the surface and set up a fatal meningitis.

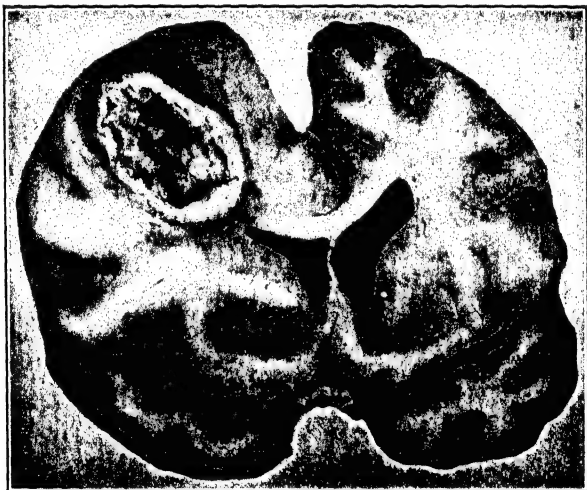


FIG. 466.—Single metastatic brain abscess in the frontal lobe secondary to an abscess of the lung. The right ventricle is dilated.

**Sinus Thrombophlebitis.**—Infection reaches the venous sinuses of the dura mater by spread from some neighboring focus. The wall of the sinus becomes inflamed (phlebitis), and thrombosis follows as a matter of course. The *lateral sinus* is infected from the middle ear and mastoid, so that this is the vessel most often involved. The *superior longitudinal sinus* is infected from erysipelas and other septic conditions of the scalp. The *cavernous sinus* is infected from septic foci in the nose, face, orbit, and sphenoidal air sinus; carbuncle of the face is especially dangerous in this respect.

The thrombosis tends to spread from one sinus to another, and from the lateral sinus down the jugular vein, which can be felt as a hard and tender cord. The infection may spread outward, causing meningitis or cerebral abscess. The great danger, however, is the softening and liquefaction which occur in the infected thrombus. At any moment a piece of the softened clot may be dislodged, carried by the jugular vein to the right side of the heart, and thence to the lungs where it is arrested. The inevitable

result is the formation of a pulmonary abscess, followed later by pyemia. For this reason ligation of the jugular vein must be done before any direct attack upon an infected lateral sinus can be attempted.

The *clinical course* of sinus thrombophlebitis is very different from that of cerebral abscess. In the former it is stormy and tempestuous compared with the calm and peace of the latter. High fever, rigors, and chills are common, owing to the continual discharge of septic material into the blood stream.

## MENINGITIS

Infection may reach the meninges by the blood stream, from the brain, or from neighboring foci of infection in the middle-ear, nasopharynx, accessory nasal sinuses, etc. Meningitis may complicate fracture of the base of the skull, particularly the anterior cranial fossa with involvement of the nasal fossæ and ethmoidal sinuses. In such cases the fatal infection may come from infected sinuses through the fracture line many years after the accident (Linell and Robinson). Almost any pathogenic organism may cause meningitis and even fungi have been known to do so, but there are only four common ones; these are the *meningococcus*, *streptococcus*, *pneumococcus*, and *tubercle bacillus*. The first three are pyogenic and cause purulent inflammation, so that the pathological changes are practically identical.

**Meningococcal Meningitis.**—This is the commonest form of meningitis. The disease is usually sporadic, but may become epidemic. For this reason it is known as epidemic cerebrospinal meningitis. The epidemiology is quite different from that of an ordinary infectious fever, for there is seldom more than one case in a family, and it is difficult to trace the contagion. The explanation is that the receptivity of the throat is high, while that of the meninges is low. There are always far more carriers than patients, and a carrier epidemic precedes and accompanies a case epidemic.

The *mode of infection* of the meninges is a matter of doubt. The disease is certainly spread from one person to another as a throat infection, as can be readily shown by taking swabs of the throats of a community during an epidemic. The difficulty is to decide by what route the meningococcus passes from the nasopharynx to the meninges. It may possibly spread through the lymphatics in the cribriform plate of the ethmoid and thus reach the subarachnoid space, but neither the organisms nor any sign of inflammation can be found in the ethmoid in fatal cases. It seems more likely that infection is by the bloodstream, for the meningococci can be found in the blood in about one-third of the early cases; sometimes, indeed, they are confined to the blood and never reach the meninges (meningococcal septicemia). It may be that the meninges are infected primarily from the blood, but it is difficult to explain the fact that in fulminant cases where the patient dies within twenty-four hours the blood and the fluid in the ventricles contain meningococci, yet the meninges are normal. It appears more likely that a metastatic focus is set up in the choroid plexus, from which the microorganisms are poured into the ventricles. First a choroiditis and then an ependymitis is produced, the cocci living on the ependymal lining of the ventricles, which is an epithelial structure like the lining of

the nasopharynx. The flow of fluid carries pus and bacteria into the basal cisterns and down the spinal canal as well as to a varying extent up into the cerebral subarachnoid space. In infants, especially those brought up on the bottle, the brain is very soft, so that the sulci and cerebral subarachnoid space are easily closed by the increased pressure, and the pus collects entirely in the basal cisterns, giving the posterior basic type of meningitis seen only in infants.

**LESIONS.**—The brain is covered with a purulent exudate, confined to the subarachnoid space and therefore most abundant in the sulci (Fig. 467). The meningeal vessels are greatly dilated. The exudate on the sur-



FIG. 467.—Acute meningococcus meningitis. The meningeal vessels are greatly dilated. Scattered over the surface are large opaque areas of purulent exudate.

face of the cerebrum is most marked in the frontal and parietal regions, but the bulk of the exudate is to be found at the base, where it fills the interpeduncular space, passes forward along the optic nerves, backward into the great cisterns and upward along the middle and anterior cerebral arteries. In the spinal canal the exudate is largely confined to the posterior surface of the cord, an effect of gravity. The ventricles are moderately dilated and filled with turbid fluid, the choroid plexus is hyperemic, and the lining of the ventricles roughened.

*Microscopically* the subarachnoid space is filled with a purulent exudate consisting of polymorphonuclear leucocytes with a few lymphocytes and large mononuclear phagocytes (Fig. 468). Fibrin is seldom marked. The vessels are greatly distended and there may be small hemorrhages. Meningococci are present both inside and outside the leucocytes. The brain and cord are not affected, although the exudate may penetrate the perivascular sheaths for a little distance. The only place where there is any inflammation is under the ependyma and in the choroid plexus.

The rest of the body shows little change, for the meningococcus has difficulty in establishing itself in the tissues, although it flourishes on the surface of the upper respiratory tract and in the ventricles and subarachnoid space. The nasopharynx shows congestion, edema, and an infiltration with lymphocytes and plasma cells. In rare cases the meningococcus may cause endocarditis, pericarditis, arthritis, adrenal hemorrhage, etc.

**CEREBROSPINAL FLUID.**—Lumbar puncture shows the pressure to be raised owing to a marked increase in the amount of fluid formed. The fluid is turbid, but in the earliest stage it may be almost clear. The protein content is high, above 0.3 per cent and sometimes as high as 0.8 per cent. The sugar is diminished and may be absent, owing to the fermentative action of the meningococcus. The film shows the cells to be polymorphonuclears, but as recovery sets in, their place is gradually taken by large mononuclear phagocytes (macrophages) and finally by lymphocytes. The meningococci are usually intracellular, but some may be extracellular. They are Gram-negative diplococci, bean-shaped and indistinguishable in smears from the gonococcus. They are seldom numerous and sometimes none can be found. A purulent fluid in which no organisms can be found is almost certainly meningococcal. When culturing the fluid, at least a cubic centimeter should be used; it is useless to take a mere loopful. When a case has been treated for some time, the fluid may remain turbid and full of pus cells though the bacteria disappear. This is due to an aseptic meningitis caused by the treatment. The result of culture rather than the gross appearance of the fluid is the true measure of the progress of the case.

**THE RELATION OF SYMPTOMS TO LESIONS.**—In severe cases there may be a hemorrhagic rash on the skin and mucous membranes. This is a septicemic manifestation, due to embolic plugging of the capillaries. Most of the cerebral symptoms, such as headache and vomiting, are due to increased intracranial pressure. Stiffness and retraction of the neck, the most characteristic part of the clinical picture, is caused by irritation at the posterior part of the base of the brain. It reaches its most extreme degree in the posterior basic meningitis of infants where the retraction may be so great that the head may actually touch the back, a condition of opisthotonos. Strabismus (squint) and diplopia (double vision) may be present due to involvement of the third, fourth, and sixth nerves at the base of the brain. The heightened intracranial pressure is due partly to an increased outpouring of fluid, partly to interference with the normal absorption from the cerebral subarachnoid space. This interference is caused by blockage of the eliminating apparatus (arachnoid villi and Pacchionian bodies) by the purulent exudate; the accumulation in the basal



FIG. 468.—Acute meningitis. The subarachnoid space is packed with inflammatory cells.  $\times 160$ .

cisterns which tends to push the brain up against the roof of the skull probably plays a part. Lumbar puncture, and still better cisternal puncture, will help to relieve this state of affairs. If the fluid is not absorbed it will accumulate in the ventricles which become dilated, but a true internal hydrocephalus due to blocking of the openings in the roof of the fourth ventricle is not common in adults. In infants it is a frequent and fatal complication, the great compressibility of the very soft brain of the infant being the most important factor.

**MENINGOCOCCAL SEPTICEMIA.**—In every case of meningococcal meningitis there is probably an element of septicemia, but the term meningococcal septicemia is usually reserved for those cases in which there is a blood infection without a corresponding infection of the meninges. It is an extrameningeal meningococcal infection. Meningitis may sometimes develop after the septicemia has been in progress for a number of weeks; this is called meningitis tarda. The course of meningococcal septicemia varies enormously. The fulminating cases may be incredibly rapid, and in these the infection may be so heavy that large numbers of meningococci can be seen in the blood smears. As Herrick remarks: "No other infection so quickly slays." In other cases the infections may go on for weeks and even months, blood cultures being repeatedly positive. In the more severe septicemic cases a hemorrhagic rash is likely to be present.

**OTHER FORMS OF SUPPURATIVE MENINGITIS.**—*Pneumococcal meningitis* may be primary or secondary to infection in the middle-ear, nasal sinuses or lung. The disease is very acute. The morbid anatomy is the same as that of meningococcal meningitis. The purulent cerebrospinal fluid contains large numbers of pneumococci, so that the diagnosis can readily be made from a smear. The fibrinogen is much increased, and the fluid may even clot spontaneously. *Streptococcal meningitis* is usually secondary to middle-ear or sinus infection, but occasionally it may be primary. The organism may be *Streptococcus hæmolyticus*, *Streptococcus viridans* or *Streptococcus mucosus*. The last-named usually comes from the ear and causes the formation of a characteristic sticky mucoid exudate. The morbid anatomy and the condition of the cerebrospinal fluid are the same as in the other two forms of acute meningitis. Streptococci are usually present in large numbers in the fluid. *Staphylococcal meningitis* is rare, and the organisms are present in very small numbers. *Influenza bacillus meningitis*, better called Pfeiffer's bacillus meningitis, is the fifth commonest form in America, although much less common in Britain. It is suppurative, commonest in children, and used to be very fatal. With broad spectrum antibiotics if the diagnosis is made early (a conveniently vague expression) it is said that the disease can be treated successfully in nearly every case. Typhoid and paratyphoid bacilli and *Bacillus coli* are occasional causes of meningitis. Still more rare are *Bacillus pyocyaneus*, *Bacillus anthracis*, *Bacillus mallei*, Friedländer's pneumobacillus, *Micrococcus catarrhalis*, actinomyces and a streptothrix.

**MENINGISM.**—This is a name given to a condition usually in children, in which the symptoms simulate meningitis but no evidence of inflammation is found. The blood chlorides are very labile in childhood. They may fall in lobar pneumonia, after attacks of vomiting and diarrhea, or owing to drinking large amounts of water in high fever. There is an accompanying fall in cerebrospinal fluid chlorides, but it may be less rapid. As a result of this lag there is an outpouring of water into the subarachnoid space (due to the lowered osmotic tension of the blood), and a heightening of intracranial pressure with symptoms suggestive of meningitis but at once relieved by lumbar puncture. The only abnormalities in the fluid are high pressure and low chlorides.

**Tuberculous Meningitis.**—Tuberculous infection of the meninges may be primary (in the sense that it is the first active lesion to manifest itself), or it may be part of a general miliary tuberculosis. The infection reaches

the brain by the blood stream, and it is usually believed that the meninges are primarily involved. It can be shown experimentally, however, that the meninges are very resistant to blood infection, even when large numbers of tubercle bacilli are injected into the carotid artery. On the other hand, they are readily infected when the injection is made directly into the subarachnoid space. Rich has shown that in many cases of tuberculous meningitis it is possible to demonstrate a tuberculous lesion in the brain, the choroid plexus, and even the meninges, and this lesion he regards as the primary source of the meningeal infection. The lesions are often multiple, but they may be no larger than a pea, so that the brain has to be cut into very thin slices if they are to be demonstrated. When one of these lesions is sufficiently superficial to discharge bacilli into the subarachnoid space or the ventricles, heavy infection of the meninges at once results (Fig. 469). The lesion may open into a blood vessel, causing general miliary tuberculosis (Fig. 470), or the Pacchionian



FIG. 469.—Small tuberculous lesion of the brain discharging into the subarachnoid space. Several giant cells can be seen.



FIG. 470.—Tuberculous lesion in the brain rupturing into a blood vessel. Giant cells can be seen in the lumen of the vessel.

bodies may be infected from the subarachnoid space and the bacilli pass in this way into the superior longitudinal sinus. Other workers do not agree with Rich, and believe that the meninges are infected from the blood stream. Beres and Meltzer examined 28 cases of tuberculous meningitis. In only 6 were there cortical tubercles which might have caused the meningitis, and in 11 there were tubercles in the choroid plexus.

**LESIONS.**—The type of lesion varies with the massiveness of the infection. If the dose is small the principal lesion is the miliary tubercle, but if it is large there may be an abundant nonspecific exudative reaction with the formation of a creamy or greenish somewhat gelatinous exudate at the base

of the brain extending from the chiasma in front to the cerebellum behind, filling up the spaces (Fig. 471) and glueing together the surfaces. The tubercles are covered up by this exudate, but they can usually be seen on the upper surface of the cerebellum, on the velum interpositum, and along the line of the vessels as they pass up to the cortex. Sometimes almost no exudate or tubercles can be detected unless a very careful examination be made of the base of the brain with a hand lens. In these cases it is difficult to understand why the patient should have died. A possible explanation is the frequent presence of microscopic lesions very close to the hypothalamus, a vital center. The convolutions are flattened and the sulci narrowed owing to the hydrocephalus which is nearly always present,



FIG. 471.—Tuberculous meningitis. The exudate covers base of brain.



FIG. 472.—Tuberculous granular ependymitis.

and which is caused by the thick exudate over the roof of the fourth ventricle. The ependymal lining of the dilated ventricles is roughened and granular ependymitis resembling that seen in cerebral syphilis is not uncommon (Fig. 472). When the brain is hardened and cut into very thin slices it is often possible to demonstrate small tuberculous lesions in the superficial part of the cortex or in the wall of the ventricle. Sometimes these lesions may be in the cord instead of the brain.

*Microscopically* the picture is a mixed one, partly tuberculous and partly inflammatory in nature. Definite, typical tubercles are usually conspicuous by their absence and the same is true of giant cells. Diffusely arranged epithelioid cells and areas of caseation necrosis are the characteristic features. Tubercle bacilli can be seen in appropriately stained sections. When the reaction is more acute the subarachnoid space is filled with lym-



phocytes, plasma cells, and polymorphonuclears, but here again patches of necrosis indicate the nature of the process. The walls of the vessels are thickened and infiltrated with inflammatory cells. The *brain* is remarkably free from inflammatory lesions, but in places the infection may extend for a short distance into the cortex. The primary focus in the brain shows a typical picture of tuberculosis with giant-cell formation. Tuberculous necrotic foci can often be found in the choroid plexus and velum interpositum.

*Streptomycin treatment*, by prolonging the survival period in those cases which do not recover, has greatly changed the picture at postmortem. Tuberculous granulation tissue replaces the cellular exudate, and this becomes converted into a dense layer of hyalinized connective tissue enclosing necrotic foci at the base of the brain. Hydrocephalus is a prominent feature due to obstruction in the aqueduct or the foramina of Luschka. In other cases the hydrocephalus is of the communicating type. Large meningeal tuberculomas composed of epithelioid tubercles with giant cells are a prominent feature, and similar large lesions are seen in the choroid plexus (Terplan). *Arterial changes*, whilst occasionally seen before the days of chemotherapy, have become of much greater importance since the use of streptomycin has so greatly prolonged the life of these patients. The acute tuberculous arteritis commonly seen in the circle of Willis is now transformed into a proliferative endarteritis with varying degrees of stenosis (Fig. 473). In some of the cases studied by Winter in my department in Toronto the structure of the vessels was so altered by tuberculous granulation tissue that they were only recognized by persistence of the internal elastic lamina. As Doniach points out, there is nothing to suggest that the intrathecal use of streptomycin is responsible for the endarteritis, which is due entirely to the prolongation of life. The great importance of the arterial lesions is that they cause multiple brain softenings, which in turn are responsible for a variety of focal cerebral symptoms. There may be massive necrosis of the corpus striatum.

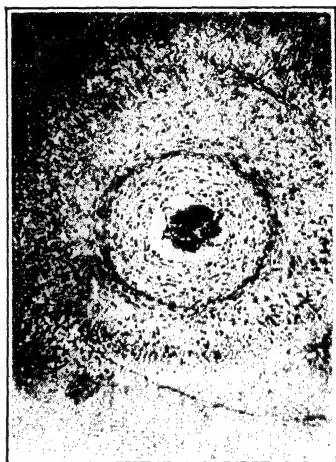


FIG. 473.—Endarteritis in treated tuberculous meningitis.  $\times 65$ .

**CEREBROSPINAL FLUID.**—The diagnosis is made by lumbar puncture, so that the changes in the spinal fluid are of great importance. The clinical picture in poliomyelitis, epidemic encephalitis, and a deep brain abscess may closely resemble that of tuberculous meningitis, and unfortunately the spinal fluid findings are quite similar, but there are slight though important differences. The pressure is raised, and the fluid is clear or opalescent, almost never turbid. When allowed to stand a fine web of fibrin forms. This is very characteristic of tuberculous meningitis and

is never seen in encephalitis and brain abscess, but a web sometimes forms in poliomyelitis and syphilitic meningitis. The *protein* is increased to a greater degree in tuberculous meningitis than in the other three (0.1 to 0.3 per cent). The *sugar* is decreased and sometimes disappears; in poliomyelitis and brain abscess it is normal, and in encephalitis it may be above normal (0.07 to 0.09 per cent). Estimation of sugar is therefore of great use in distinguishing between these easily confused conditions. The *chlorides* are low, below 0.65 per cent (normal: 0.72 to 0.75 per cent). This is the most valuable of all the chemical tests, for no other condition gives a really low reading. In exceptional cases the chlorides may be normal. The *cells* average from 50 to 200 per c.mm. (normal: 5 or less, though in children it may be higher). The cell count is usually below 50 in encephalitis and brain abscess, but in poliomyelitis it may be similar to tuberculous meningitis. The predominant cell is the lymphocyte, but in acute reactions, especially in children, there may be as many polymorphonuclears as lymphocytes. The demonstration of the *tubercle bacillus* is the conclusive proof of the nature of the condition. Both the web and the centrifuged deposit should be examined.

**THE RELATION OF SYMPTOMS TO LESIONS.**—Paralysis of the cranial motor nerves, especially the oculomotor, may be caused by the exudate at the base of the brain, so that ptosis (drooping of the upper lid), squint, and diplopia are common. Stiffness and retraction of the neck are symptoms common to any meningeal irritation involving the base of the brain and the upper spinal meninges. Cortical irritation may lead to spasms and convulsions. The acute hydrocephalus which is of such constant occurrence is responsible for symptoms of compression terminating in coma.

The work of Smith and Vollum on the treatment of tuberculous meningitis by the combined intrathecal use of streptomycin and tuberculin is suggestive from the standpoint of general pathology. The satisfactory results which attend this method of therapy in some cases are believed to be due to disappearance of the granulomatous exudate at the base of the brain. Apparently the tuberculin causes this exudate to resolve; the bacilli which are thus liberated are killed by the streptomycin. It is intriguing to recall that in 1890 Robert Koch used these words when he first announced the discovery of tuberculin: "There is no question of a destruction of the tubercle bacilli in the tissues, but only that the tissue enclosing the tubercle bacilli is affected by the remedy. The remedy does not kill the tubercle bacilli but the tuberculous tissue."

**Tuberculoma.**—This is a rather rare slow-growing circumscribed tuberculous lesion, often multiple, usually occurring in children, and easily mistaken for a tumor of the brain. It may become as large as a walnut (Fig. 474). It generally forms a firm spherical mass, but softening may sometimes occur with the formation of a tuberculous abscess. *Microscopically* the center is caseous, with epithelioid and giant cells at the margin. The prognosis is bad, for operative interference is nearly always followed by tuberculous meningitis or general miliary tuberculosis.

**TUBERCULOMA EN PLAQUE.**—Tuberculoma en plaque is a very rare tuberculous lesion occurring only in adults. There is a tuberculous meningo-encephalitis of very chronic character, with the formation of a flat plaque on the surface of the fronto-parietal cortex. The symptoms are those of tumor, *i.e.*, headache, vomiting and Jacksonian epilepsy, with the addition of fever.

**TORULA MENINGITIS.**—This is a very rare condition due to torula infection, a yeast belonging to the group Blastomycetes. The cerebral lesion is a meningo-encephalitis, and the infection is secondary to a lesion in the lung or elsewhere.

The lesions may simulate those of tuberculosis, consisting of epithelioid cells and giant cells, but the characteristic feature is the presence of large numbers of yeast-like cells.

**LYMPHOCYTIC CHORIOMENINGITIS.**—Under this heading are placed cases of acute but mild meningitis, characterized by a remarkable lymphocytosis. The cell count may be as high as 600 per c.mm. The fluid is sterile, with a slight increase of protein but normal sugar and chlorides. The Wassermann reaction is normal, but the colloidal gold test may give a meningitic or even a paretic curve. The patients all recover, so that the condition is also called *benign lymphocytic meningitis*. The condition is now known to be due to a virus, as can be shown by inoculating monkeys with the cerebrospinal fluid. Incidentally this is about the only virus disease of the nervous system in which the virus can constantly be recovered from the cerebrospinal fluid. In the experimental animal the choroid plexus as well as the meninges are inflamed. The distribution of lesions in man is not known, as the disease is not fatal. The virus seems to occur naturally in mice without producing disease, and it is possible that it may be transmitted from mice to man.



FIG. 474.—Tuberculoma of the brain.

## VIRUS DISEASES OF THE NERVOUS SYSTEM

Certain filterable viruses have a special affinity for the central nervous system. They are neurotropic and cause some of the most serious diseases which afflict that system. There are some viruses which primarily attack the nervous system, *e. g.*, poliomyelitis, rabies, distemper of dogs, Borna disease of horses. Others do not ordinarily involve the nervous system, but when injected into the brain of an animal they produce serious or fatal results; examples are herpes febrilis, salivary gland disease of guinea-pigs, and vaccinia. There is still a third group of very common febrile diseases (measles, chickenpox, smallpox, vaccinia) in which injury of the nervous system occurs on rare occasions, usually during convalescence. Neurotropic viruses are peculiar in that they reach the central nervous system *via* peripheral nerves (cranial and spinal), traveling actually in the axis cylinder of the nerve fiber. Moreover they diffuse throughout the entire nervous system (central, peripheral and visceral), as bacteria spread throughout the vascular system in septicemia. Thus, when the virus of

rabies is inoculated into the brain it can be recovered from the peripheral nerves some days later, although if a nerve is cut across, the distal part remains free from infection. That the virus travels by way of the axons is demonstrated by the fact that when the virus of poliomyelitis is inoculated into the sciatic nerve of one leg it can be recovered from the opposite motor cortex, thus following the decussation of the motor path.

The three cardinal lesions of virus diseases of the central nervous system are inclusion bodies, cellular necrosis, and inflammation. Not all of these need be present, and unfortunately none of them is specific for viruses. It is very difficult to say how long a virus may remain in the nervous system once it has gained entrance. There may be more than fancy in von Economo's conception of the "encaged virus," which once having got in cannot get out again. It may do no harm until some accessory factor takes a hand, as in the case of herpes febrilis. Many of the viruses produce inclusion bodies in the affected nerve cells, *e. g.*, rabies, poliomyelitis, and Borna disease of horses. These and other fundamental matters have already been considered in the general discussion on viruses in Chapter 7.

Reference has already been made to the way in which neurotropic viruses travel along nerve fibers. This ability depends to some degree on the age of the individual. A neurotropic virus, which in young mice can travel from the nose to the olfactory region of the brain and thence to the thalamus and cortex causing fatal encephalitis, is held up in the olfactory region in older animals. This is probably due to the gradual development of a local immunity to the virus.

Two great classes of lesions produced by neurotropic viruses may be distinguished. (1) Non-suppurative encephalitis or myelitis in which the infecting agent enters and *destroys certain groups of nerve cells*. Poliomyelitis, rabies, herpes, louping ill in the sheep, Borna disease in the horse (equine encephalomyelitis) are characteristic examples; epidemic encephalitis may be included with reserve, and possibly herpes zoster. (2) Encephalomyelitis in which the essential lesion is a *primary demyelination of nerve fibers*. The evidence that this group is caused by a virus is not absolute, only suggestive. An acute disseminated encephalomyelitis of this type may be primary, or it may follow the specific infectious fevers or vaccination. The demyelination, shown by the Weigert-Pal method, is striking and widespread. The question naturally suggests itself as to whether such demyelinating diseases as disseminated sclerosis and Schilder's disease should be included in this group. These latter diseases, however, are slowly progressive, whereas encephalomyelitis, if not fatal, ends in recovery. Our knowledge regarding the essential mechanism of demyelination and the question whether it is due to one or several classes of agent is still too rudimentary to justify us in concluding that it is due to a virus infection in every instance. In addition to the destructive and demyelinating lesions, both groups show perivascular collections of round cells. In Group I at least a proportion of these represent a true inflammatory reaction to the virus, all the more likely because polymorphonuclears are abundant in so typical an example as poliomyelitis. In Group II they are probably secondary to the myelin destruction, being proliferated microglial scavengers.

**Acute Anterior Poliomyelitis.**—Poliomyelitis or infantile paralysis is an acute infectious disease of the central nervous system which may appear in endemic or in epidemic form. It is a disease of young children, not of infants as the name would suggest, but in the large Winnipeg epidemic of 1928, 20 per cent of the cases were over fifteen years of age. In recent outbreaks many adults are affected. An epidemic usually begins about the end of June and disappears with the first onset of cold weather. In spite of this clear-cut seasonal incidence which suggests an insect carrier, there seems to be little doubt that the disease is spread by personal contact. The carrier is not a patient, but a healthy person who harbors the virus in his nasopharynx or intestine. When a person develops the disease the virus in the throat at once loses its virulence, so that there is little danger of infection from the patient himself. More than one case seldom develops in a household. An epidemic of poliomyelitis is preceded by a carrier epidemic during which the virulence becomes raised. When this becomes sufficiently high, invasion of the nervous system occurs and a true epidemic begins, lasts a few months, and then rapidly disappears. During an epidemic the incidence of infection is much greater than the incidence of the disease.

**Pathogenesis.**—Poliomyelitis is caused by a filter-passing virus. The bacteriology has already been discussed in Chapter 7. The virus is strictly neurotropic. The disease can be reproduced in the monkey by intracerebral inoculation of infected spinal cord. At least one human strain (Lansing strain) has been transferred through the monkey to the cotton rat and then to white mice (Armstrong). It is of interest to note that the virus is now non-pathogenic for the monkey and can be used for immunization. The monkey can be infected by painting the virus on the nasal mucosa. As no infection occurs when the olfactory nerves are cut, it is evident that infection passes along these nerves to the olfactory bulbs, which show marked inflammatory and degenerative lesions, and thence to the brain and spinal cord. These results have been applied to man, and it has long been presumed that the portal of entry was the nasopharynx and the olfactory tract. On the other hand it is now admitted that no lesions are found in the human olfactory bulbs, nor does blockage of the olfactory route by spraying the roof of the nasal passages with zinc sulphate offer any protection, although this procedure protects the monkey against infection from the nasopharynx. Yellow fever and rabies, both virus diseases, can be transmitted to the monkey by the nasal route, but no one suggests that this is the usual method of infection in man.

It is now known that the poliomyelitis virus can be isolated from the stools both in active and convalescent cases, sewage, the wall of the small and large intestines, and the mesenteric lymph nodes (Paul and Trask). During the first week it is present in the stools in from 70 to 90 per cent of cases, and they remain infective for many weeks. These results suggest that poliomyelitis is primarily an intestinal rather than a respiratory tract disease. This would agree with the seasonal incidence. Infection may occur by ingestion of infected material, but the infection may take place from the pharynx over which all food must pass. There is no *proof* that infection occurs from the intestine, either in the monkey or man.

From the standpoint of the human disease the most important contribution is that of Faber and Silverberg, who traced the course of the virus in eight patients dying in the acute stage by studying the distribution of the lesions demonstrated histologically. In general the evidence of penetration through the upper alimentary and respiratory tracts was far more striking than through the lower alimentary tract. The pharynx, which is exposed to infection both from the nose and the mouth, was a specially favorable source for penetration of the virus. There was no single portal of entry, nor any support of the concept of an exclusive channel for all cases such as the olfactory and the intestinal. In no instance was the olfactory tract the route of infection. Invasion through the sympathetic results in initial involvement of the central nervous system at the spinal level; invasion through the other principal channels (the fifth, ninth and tenth cranial nerves) results in initial involvement at the level of the brain stem (midbrain, pons, medulla). This does not necessarily determine the site of initial paralysis.

The suggestion that poliomyelitis is primarily an intestinal rather than a respiratory tract infection has directed attention to the possibility of insect vectors. It was soon found that the virus could be demonstrated in the bodies of green bottle and blow flies caught in epidemic areas and near the dwellings of poliomyelitis patients (Trask and Paul). On the basis of these experimental facts it has been suggested that human infection is mainly carried by flies. It seems probable that infection in the main is by a stool-borne virus from patients and healthy carriers, rather than by droplets from the nose and mouth. These theoretical considerations are of profound importance in the effort to prevent the spread of poliomyelitis during an epidemic. If infection is from intestinal discharges there is no more point in avoiding large crowds or closing moving picture theatres, schools and churches than there would be in the case of typhoid fever. Indeed the same precautions would seem to be desirable in the two diseases. The history of the experimental work on poliomyelitis shows that the fact that a disease or lesion can be produced in a certain way in an experimental animal is no proof that it is produced in that way in man. The immunity which follows the disease is life-long, thus agreeing with the rule of virus diseases in general. A second attack is very rare. Immune bodies can be demonstrated in the blood of the patient during the remainder of his life.

It is possible that the attack of the virus may not be limited to the motor nerve cells, but that it may include the nerves and the muscles, especially the motor end plates. The lesions observed in the muscles are not the same as those produced by surgical division of nerves, in which the changes do not begin in the end plates but involve all parts of the nerves simultaneously.

**SYMPTOMS.**—Although the disease is called infantile paralysis there may be no paralysis. These cases are spoken of as abortive forms; they remain in the pre-paralytic stage. Perhaps immunity develops in time to prevent the paralytic lesion. The child is feverish, irritable, with rigidity of the neck and a stiff back. The diagnosis in this stage depends on a healthy clinical suspicion and lumbar puncture. When paralysis develops, usually on the second or third day, it attains its maximum at once, and as a rule shows no subsequent extension. This again may be attributed to the rapid immunity. Only one arm or leg may be involved,

or both legs (paraplegia). There may be bulbar symptoms with facial paralysis, squint, difficulty in swallowing, and respiratory failure. In the bulbar type there may be no spinal symptoms. In the fatal cases there is often a marked rise of blood pressure. In addition to motor weakness, pain is a constant symptom. This is usually pain on passive movement, but there may be spontaneous pain in a limb.

**LESIONS.**—The lesions are always widely distributed throughout the central nervous system, although the symptoms (monoplegia, etc.) may suggest a very limited involvement. The lumbar enlargement of the cord is the most frequent site of lesions, followed by the cervical enlargement. The most marked lesions are in the anterior horn, but the posterior horn is also involved. Although the disease is called a myelitis, the brain is invariably involved in cases that come to autopsy. The severe cerebral lesions are confined to the brain stem (medulla, pons, and midbrain), they are slight or absent in the basal ganglia, and practically never found in the cerebral cortex. Ependymitis in the floor of the fourth ventricle is not infrequent. In addition to the cord lesions there is involvement of the dentate nucleus of the cerebellum, the Gasserian ganglion, posterior root ganglia, and anterior and posterior nerve roots. It is evident that the virus has spread far and wide through the central nervous system. The lesions are both inflammatory and degenerative. The inflammatory lesions are the result, not the cause, of the degeneration. Sometimes, however, as in the brain stem, inflammation may be much more evident than any demonstrable neuronal degeneration.

The cord is swollen on account of edema, and bulges when cut across. The gray matter may be hyperemic. The meninges are congested and may show slight inflammatory change, but this is seldom marked, thus agreeing with the absence of marked cellular changes in the cerebrospinal fluid. The so-called meningeal symptoms characteristic of the preparalytic stage are apparently not due to meningeal inflammation, as can be shown convincingly in the experimental animal.

The *inflammatory lesions* are best studied in the gray matter of the anterior horn of the spinal cord (anterior poliomyelitis) and in that of the pons and medulla, but the white matter does not escape. There is great congestion and hemorrhages are frequent. The vessels are surrounded by collars of inflammatory cells similar to the perivascular collars in epidemic encephalitis. In addition to the perivascular lesions, diffuse and focal collections of inflammatory cells are present in the interstitial tissue. The focal collections may show necrosis. For the first few days the inflammatory cells are polymorphonuclears. These are then replaced by small round cells which have the appearance of lymphocytes, but when stained with silver they are seen to be microglia. Only the naked nuclei are stained in a hematoxylin and eosin preparation, but the silver brings out all the characteristic processes of the microglia cell. There is an enormous proliferation of microglia at an early stage of the disease; many of the cells lose their processes and become converted into neuronophages (see below). The astrocytes do not proliferate in the acute stage, but form the subsequent scar.

The *degenerative lesions* chiefly affect the motor cells of the anterior horn of the spinal cord, although the cells of the posterior horn, Clarke's column, and the posterior root ganglia may also suffer. Every degree of degeneration may be seen, from loss of Nissl's granules (chromatolysis) and eccentricity of the nucleus to complete disappearance of the cell (Fig. 475). Not a single ganglion cell may be seen in the section. The process of cell death and disintegration may be incredibly rapid, as can be seen in the experimental animal. This agrees with the suddenness and completeness of the paralysis. The dead cells may be surrounded and



FIG. 475.—A large degenerated ganglion cell in poliomyelitis. The cell has lost its nucleus and its Nissl's granules.  $\times 600$ .

invaded by phagocytes, a process known as neuronophagia. Most of the neuronophages are Hortege cells (microglia), but some polymorphonuclears may be seen. Degenerative changes are never marked in the brain, although the inflammatory lesions may be severe. Intracellular inclusions are present in degenerating nerve cells in the early stage, but not when the cell has become necrotic (Hurst); the material must be fixed in sublimate formol and stained with Giemsa or eosin-methylene blue.

The nerves show early demyelination and relatively minor changes in the axis cylinders. The lesions in the nerves are less severe and extensive than those in the muscles. It is possible that the virus may act directly on the nerves and even on the muscles (Denst and Neuburger).

It would appear from the important work of Carey and his associates that one of the earliest changes is in the motor end plates when stained by

the gold method, particularly in the respiratory muscles such as the diaphragm and intercostals. This change varies from a granular degeneration to complete dissolution. In the intercostal muscles of a girl, aged three, who died within thirty-six hours of the onset of symptoms, there was complete absence of motor end plates in 5978 denuded axons among 6109 that were counted. The motor axons degenerate, and it is important to note that the spread is centripetal, not centrifugal as when a motor nerve is severed. All this suggests that the virus may attack the nerve endings independently of the attack on the motor cells in the spinal cord.

The *end result*, seen when the cord is examined long after the acute illness, is atrophy of the anterior horn on one or both sides. The nerve cells are replaced by astrocytes, and there is well-marked gliosis and fibrillar formation. The motor fibers arising from the destroyed cells disappear,



as can be seen in sections stained with Weigert's myelin sheath stain. The paralyzed muscles show atrophy, fatty infiltration, and replacement by connective tissue.

Focal myocarditis can frequently be demonstrated if multiple sections of the heart are examined (Dolgopel and Cragan). In some of these cases death is due to cardiac failure. The cells of the exudate may be chiefly polymorphonuclears, lymphocytes or mononuclears.

**THE RELATION OF SYMPTOMS TO LESIONS.**—There is little or no opportunity for autopsy examination in the preparalytic stage, but observations on the experimental animal suggest that the so-called *meningeal irritation* (stiffness of the neck, irritability) is not due to inflammatory changes in the meninges, in spite of the fact that the cell count in the spinal fluid is highest at this stage. The initial "*systemic*" symptoms, such as fever, drowsiness, anxiety, heightened sensibility to pain, headache, and vomiting, may be explained by involvement of the thalamus and hypothalamus. The *pain* is probably due to lesions in the posterior root ganglia and in the posterior roots themselves. The *paralysis* is easily explained by the destruction of the motor cells in the anterior horn. Groups of motor cells may be picked out while neighboring groups are spared, and the lesions may be much more marked in the anterior horn on one side or may be confined to that side. This serves to explain the fact that the paralysis may be confined to one limb or even to one muscle or group of muscles. Facial nerve palsy and paralysis of other cranial nerves are due to lesions in the brain stem. Difficulty in swallowing with regurgitation of fluids through the nose (paralysis of the palate), respiratory failure (to which death is usually due), and other signs of bulbar paralysis are caused by lesions in the medulla. The *increased blood pressure* is due to bilateral nerve cell degeneration in the reticular formation of the medulla in an area corresponding with the upper half of the fourth ventricle (Löblich).

**CEREBROSPINAL FLUID.**—The cerebrospinal fluid shows changes resembling those of epidemic encephalitis and tuberculous meningitis, but with certain differences. The fluid is clear or slightly opalescent, and occasionally a fine web may form, such as is seen in tuberculous meningitis but which never occurs in encephalitis. In the preparalytic stage the cells are high and the globulin low. As the disease progresses the cells fall and the globulin rises. In the Winnipeg epidemic of 1923, 80 per cent of the cases had a cell count between 10 and 200. The cells are mainly lymphocytes, but in the earlier stages there may be over 50 per cent polymorphonuclears. The sugar and chlorides are unchanged. In the Winnipeg cases a mid-zone reaction with the colloidal gold test was common.

**COXSACKIE VIRUS DISEASE.**—In 1947 Dalldorf isolated a virus from patients in the village of Coxsackie in New York State which was apparently a cousin of the poliomyelitis virus and yet different from it in some important respects. The main biological character of this virus is that it is pathogenic only for suckling mice and hamsters, not for older animals of these species nor for monkeys. It has therefore been called the suckling mice virus. The primary lesion in the mice seems to be in the skeletal muscles, the fibers of which undergo marked degeneration with proliferation of the cells of the sarcolemma sheath. Necrotizing lesions are also present in the myocardium, central nervous system, liver, pancreas and fat (Godman *et al.*). This virus and other close antigenic relatives have been isolated from the stools and nasopharyngeal secretions of patients with signs of meningeal irritation and diagnosed as nonparalytic poliomyelitis and aseptic meningitis. The virus is widely distributed in the United States, and Rhodes and his associates have isolated both Coxsackie and poliomyelitis viruses from children and adult contacts in Toronto. It has now been established that there are at least two types of the virus: Group A,

which causes myositis in mice, and Group B, which produces inflammation (encephalitis) in the central nervous system and in fat.

**THEILER'S DISEASE.**—In 1938 Theiler described a form of spontaneous encephalomyelitis in mice due to a virus. The disease is of interest because it bears a striking resemblance to human poliomyelitis (it has been called "poliomyelitis of mice"), and because the virus is found in the intestine of normal mice. An analogy may be drawn between these facts and the theory that poliomyelitis is primarily an intestinal infection.

**Encephalitis.**—Inflammation of the brain may be bacterial or viral. Bacteria cause a *suppurative encephalitis* in the form of small abscesses scattered throughout the brain, which may be microscopic or visible to the naked eye. This occurs in pyemia due to various pyogenic bacteria, and in bacterial endocarditis, where the lesions are often microscopic. Such conditions are terminal, and therefore not of great clinical interest.

*Virus encephalitis* constitutes a group of diseases, some of which are epidemic. In some the lesions represent a non-suppurative inflammation characterized by perivascular collections of macrophages, lymphocytes and plasma cells with accompanying degeneration of nerve cells. In others, particularly the postinfectious types, demyelination is the outstanding feature. The principal examples of virus encephalitis are: (1) type A encephalitis (von Economo), (2) type B encephalitis (St. Louis), (3) equine encephalomyelitis, and (4) acute disseminated encephalomyelitis.

**Type A Encephalitis.**—This is also known as epidemic encephalitis and encephalitis lethargica. Other forms of encephalitis may be epidemic associated with lethargy, and as this type was first described by von Economo in Vienna in 1917, it is often known by his name. It appeared like a bolt from the blue in 1917, spread all over the world in pandemic form, returned more than once to a locality, and then vanished. Fresh cases are very seldom seen now. On general grounds it must be assumed that the disease is due to a virus, but this has never been proved.

**SYMPTOMS.**—To attempt to give an adequate account of the symptomatology of epidemic encephalitis would be ludicrous in a textbook of pathology, for almost every known neurological symptom may be produced. Moreover the epidemic gradually changed its clinical manifestations. Winnipeg was visited by two epidemics, both of which I studied, the first in the winter 1919–1920, the second at the beginning of 1923. In the *first epidemic* the patient was dull, lethargic, somnolent, and showed oculomotor disturbances. He would lie like a log in bed with drooping lids or closed eyes, the lines of expression all ironed out, sunk in a stupor which no external stimuli could penetrate, the flash and speed of the mind gone, the dim rushlight of reason hardly flickering. In the *second epidemic* the picture had changed completely. Body and mind were now keyed to full activity. The muscles were in a state of constant movement, which was paralleled by a condition of mental excitement. Words came in a torrent, rationally at first, but drifting away into delirium. Occupation formed the main topic of conversation: the teacher was continually teaching, the merchant was casting up accounts, the builder planning new houses. The first picture was akinetic, the second hyperkinetic. It must be noted, however, that more than one-half the 1923 cases developed lethargy and somnolence sooner or later.

In addition to fever and somnolence, oculomotor palsies were extremely common, causing diplopia, strabismus, and ptosis. The hyperkinesia manifested itself by every variety of choreiform and athetoid movement, as well as clonic spasm of

various kinds. Rigidity, a "muscle-bound" condition, was present in the acute stage, but was far more pronounced in chronic encephalitis, giving the well-known condition of Parkinsonism or postencephalitic paralysis agitans, with its mask-like face, stoop, flexed arms and wrists, and mincing steps. Some 20 per cent of the cases developed some degree of Parkinsonism. Other postencephalitic conditions which may be mentioned were narcolepsy and oculogyric crises (sudden attacks in which the eyes are fixed in a conjugate position). Among the most distressing of the sequelæ in children were profound emotional and moral disturbances, with disintegration of the mind and character.

**LESIONS.**—The gross appearance of the brain is not characteristic. Microscopically the chief lesion is the familiar perivascular collars of chronic inflammatory cells (Fig. 476). In contrast to poliomyelitis there



FIG. 476.—Epidemic encephalitis. Collar of cells around inflamed vessel in floor of fourth ventricle. The cells are in the true perivascular space.  $\times 200$ .

are no polymorphonuclears, no inflammatory foci, no areas of necrosis. Congestion is marked, and small hemorrhages are frequent. The lesions are most numerous in the periaqueductal region of the midbrain, but they are also marked in the basal ganglia, pons and medulla. The cerebral and cerebellar cortex are not affected. Degeneration and disappearance of the pigmented cells of the substantia nigra in the midbrain is a striking feature in the chronic stage, and there is also cellular degeneration in the globus pallidus. These structures are stations on the extrapyramidal tract, the primitive motor pathway, and the lesions serve to explain the motor helplessness and rigidity.

The *cerebrospinal fluid* shows no characteristic changes except that the sugar content tends to be high, due to an accompanying hyperglycemia.

**TYPE B ENCEPHALITIS.**—During the fall of 1933, an epidemic of encephalitis broke out in St. Louis and the surrounding district, which has been called encephalitis B. There was a recurrence in 1937. While resembling lethargic encephalitis, it appears to be more closely related to an epidemic reported from Japan in 1924. Indeed, it is identical with the latter clinically and pathologically, although it reacts differently serologically. The disease differs from the lethargic forms in the following respects. Somnolence is uncommon, convulsions are frequent, there is a remarkable absence of the usual oculomotor palsies (ptosis, strabismus, diplopia), there are no sequelæ, the lesions are at higher levels (frequently in the cerebrum), there is no special localization in the midbrain. Monkeys and mice are successfully infected by intracerebral inoculation of brain tissue and also by the intranasal route. The St. Louis convalescent serum protects these animals against the St. Louis virus, but not against the virus from the Japanese cases. The disease is probably transmitted by mosquitoes.

**EQUINE ENCEPHALOMYELITIS.**—Horses suffer a fatal form of encephalomyelitis, a virus disease which appears in epidemic form. In 1938 there was a widespread epidemic of this disease in the United States and Canada. In a number of instances persons, particularly children, fell ill on farms where there were sick horses, and in fatal cases the same virus was found in the human patient and the horse. The human disease runs a very severe clinical course, with a fairly high cell count in the cerebrospinal fluid. In the late summer and during the autumn of 1941 over 1000 cases occurred in Manitoba and Saskatchewan due to the so-called Western strain of virus, and 1080 cases in North Dakota. At autopsy the picture is that of an acute disseminated encephalomyelitis with intense congestion, perivascular collections of polymorphonuclears, and in places an acute arteritis. In addition there is neuronal degeneration and areas of actual necrosis. The lesions are widely distributed throughout the cortex, basal ganglia, pons, medulla, and cervical cord. The polymorphonuclear exudate is reflected in the cerebrospinal fluid, which shows a high cell count in which from 60 to 90 per cent of the cells may be polymorphonuclears.

The disease is readily transmissible to mice by intracerebral injection of brain tissue. Human infection is probably due to mosquitoes, but this has not been proved. Specific antibodies are found in the blood of domestic birds and mammals during an epidemic. Chickens and pigeons seem to serve as a reservoir of the infection. The virus can be transmitted to these birds not only by mosquitoes but also by ticks. The latter vector can pass on the virus to their offspring for innumerable generations. The evidence is conclusive that this is a virus disease; this is not true of the lethargic form of encephalitis.

There are two varieties of the disease, known as Eastern and Western. The Eastern form, prevalent in the Atlantic states, is the more virulent. Horses can be protected by a vaccine of virus grown on chick-embryo.

**ACUTE DISSEMINATED ENCEPHALOMYELITIS.**—The very occasional development of encephalitis as a result of one of the infective fevers has long been recognized. During recent years there has been a marked increase in the number of cases of acute and widespread involvement of the central nervous system either following some febrile disorder or occurring spontaneously. As these cases all have a similar if not common pathology, characterized by scattered patches of perivascular demyelination associated with an inflammatory reaction, they may conveniently be considered under the heading of acute disseminated encephalomyelitis. Three main types may be distinguished: (1) post-vaccinal encephalitis, (2) encephalitis following infectious fevers, and (3) spontaneous encephalomyelitis.

*Post-vaccinal encephalitis* has come into prominence since 1922, particularly in England and Holland. It is the most dangerous form of disseminated encephalomyelitis, with a mortality of from 25 to 50 per cent. The incidence in England is

1 in 50,000 vaccinations, while in Holland it is 1 in 5000. The onset, usually about the eleventh day after vaccination, is acute and the course rapid, with fever, vomiting, headache, squint, and sometimes upper motor neurone paralysis. It is possible that the vaccine virus is not directly responsible for the encephalitis, but may activate a virus lying dormant in the body. This is not so far-fetched as it sounds, for it is known that 80 per cent of normal guinea-pigs harbor a virus in the salivary glands, which when injected into the brain produces a fatal encephalitis (Cole and Küttner).

*Encephalitis following fevers* is most often a sequel to *measles*. More rarely it follows other virus diseases such as mumps, chicken-pox, and whooping cough. Post-measles encephalomyelitis may be more of a myelitis than an encephalitis. The characteristic symptoms are paraplegia, first flaccid and later spastic, incomplete or dissociated anesthesia, and loss of sphincter control. Fortunately these symptoms are usually only temporary.

*Spontaneous encephalomyelitis* is another disease of the central nervous system which has become considerably more common in recent years. It is often mistaken for epidemic encephalitis, but the prognosis is very much better, for recovery is the rule and serious sequelæ are quite uncommon. In adults the clinical picture suggests a myelitis, while in children it is more a meningoencephalitis. In the cerebral form there are symptoms of meningeal irritation, convulsions, or hemiplegia. Even with marked meningeal symptoms the cerebrospinal fluid is often normal, but the cell count may be increased. The spinal symptoms are pain and paresthesias in the legs, weakness and even temporary paralysis of the legs, with loss of the deep reflexes but a positive Babinski sign. Nystagmus is common, but diplopia, so characteristic of epidemic encephalitis, is very rare and the cranial nerves usually escape.



FIG. 477.—Post-vaccinal encephalomyelitis; myelin sheath stain.  $\times 7$ .

**LESIONS.**—In all forms of acute disseminated encephalomyelitis the essential lesion is perivascular demyelination (Fig. 477). The lesions are scattered in patchy form through the gray and white matter of the brain and cord. They are most marked in the pons, medulla, and the lumbar region of the cord, in contrast to the lesions of epidemic encephalitis which are most numerous in the midbrain. The demyelination is best seen when the tissue is stained with iron hematoxylin or Weigert's myelin stain, the lesions standing out as pale patches on a black background. These lesions are very similar to those of disseminated sclerosis, but the removal of the myelin is extraordinarily rapid. Perivascular inflammatory cells are also present and these cells may form a broad zone outside the adventitia extending for some distance into the brain substance, quite unlike the compact collars of cells seen in epidemic encephalitis. The pale areas may contain many scavenger cells (compound granular corpuscles) derived from the microglia.

**Rabies.**—Rabies or hydrophobia is an acute inflammatory disease of the nervous system, which is transmitted to man by the bite of a rabid animal, usually a dog, sometimes a wolf. It is caused by a filter-passing virus, and it has already been considered in connection with virus diseases in Chapter 7. In this place it is sufficient to recall that the virus passes along the axis cylinders of the nerves to reach the central nervous system, in this respect resembling the virus of poliomyelitis and herpes simplex. The characteristic cytoplasmic inclusion bodies (Negri bodies) are found in the nerve cells of the Hippocampus major, medulla and cerebellum.

**HERPES.**—Like rabies, poliomyelitis, and probably epidemic encephalitis, herpes is a disease caused by one of the filter-passing viruses. It is characterized by the formation of small vesicles. There are two distinct forms: (1) herpes zoster or shingles in which the vesicles follow the distribution of a sensory nerve, and (2) herpes simplex in which there is no such distribution. An attack of the former is followed by lasting immunity, but in the case of the latter there is no immunity. They are all caused by entirely different viruses.

**Herpes Zoster.**—This is an inflammatory condition of the posterior root ganglia or the Gasserian ganglion. It is the sensory analogue of poliomyelitis: the type of lesions in the nervous system and the condition of the cerebrospinal fluid is the same in the two diseases. Usually only one ganglion is involved, most often in the dorsal region. The eruption is always unilateral, running in a zone (zoster) as far as the middle line, and is preceded by neuralgic pains, which in old people may be very persistent and severe. The vesicles begin as papules, and may leave some scarring. The lesions in the ganglia are similar to those in the anterior horn in poliomyelitis, i.e., congestion, hemorrhage, perivascular collections of lymphocytes, and degeneration of ganglion cells with neuronophagia. There is Wallerian degeneration of the nerve fibers in the posterior roots, in the peripheral nerves, and in the posterior columns.

Intranuclear inclusions have been found not only in the dorsal root ganglia and sympathetic ganglia, but also in the esophageal mucosa, the myenteric plexus of the stomach, and in the cells in necrotic focal lesions in the pancreas, adrenal and ovary (Cheatham). It would appear that the distribution of the virus may be widespread and that it enters the body by the sympathetic nerves of the respiratory and gastrointestinal tracts, migrates to the dorsal root ganglia, and reaches the skin by centrifugal spread along the peripheral nerves. The visceral and cutaneous lesions resemble those of varicella, and it is probable that the viruses of the two diseases are identical, the varicella lesions resulting from hematogenous spread in a non-immune person, whilst those of zoster result from neurogenous spread in a person with humoral immunity.

**Herpes Simplex.**—This is the common form of herpes which may complicate pneumonia and other fevers (herpes febrilis). It usually occurs on the lips (herpes labialis), but may be on the cornea or external genitals. It differs from herpes zoster in being recurrent, not following the line of nerves, and causing no change in the cerebrospinal fluid. When the virus of herpes simplex is inoculated into the cornea of a rabbit it sets up a fatal encephalitis. In whichever part of the body the virus is inoculated, it passes along the axis cylinders until it reaches the central nervous system, where its presence can be detected by the appearance of the Lipschutz bodies which have already been described in Chapter 7. These bodies are found in the epithelial cells at the site of inoculation (skin, cornea), as well as in the nerve cells. The lesion in man is inflammation of a sensory nerve ganglion.

**LOUPING ILL.**—Although this is a virus of sheep, it may be considered here because of the interest of its lesions. As the Scotch name indicates, it is characterized by progressive incoördination and cerebellar ataxia. The disease can be reproduced

both in the mouse and monkey. In the monkey there is a diffuse encephalomyelitis, but the principal lesion is a massive destruction and astonishing disappearance of the Purkinje cells of the cerebellum. The virus has the same strange selective action on these cells as the virus of poliomyelitis has on the motor cells of the anterior horn of the spinal cord. Laboratory workers in contact with the virus are said to have developed mild infections.

### NON-VIRAL TYPES OF ENCEPHALITIS

**LEAD ENCEPHALITIS.**—In the chronic lead poisoning of children (see Chapter 13), one of the most dreaded complications is lead encephalitis. This differs from other varieties of encephalitis in that it takes the form of an extreme cerebral edema caused by the presence of lead in the brain. A similar condition can be produced experimentally in animals by the continued administration of small quantities of lead. The brain is remarkably swollen, the cerebral convolutions are flattened, the ventricles are compressed, and the medulla is pressed down into the spinal canal. The cerebrospinal fluid pressure may be 700 mm. of water as compared with the normal pressure of 120 mm.



FIG. 478.—Cerebral toxoplasmosis.



FIG. 479.—Mammillary body in Wernicke's encephalopathy.

**CEREBRAL TOXOPLASMOSIS.**—Although this condition is caused by a protozoön parasite, *Toxoplasma* (page 196), it may be considered here. The infection occurs mainly in the newborn and young children (intra-uterine infection), but occasionally in adults. In the newborn the protozoa probably come from the mother who has a smouldering low-grade infection. At a later age it seems likely that the source of infection is an eye affected by toxoplasmosis. In children the clinical picture is that of encephalitis, but in adults, in spite of the presence of focal necrotic lesions in the brain, there are usually no cerebral symptoms. The lesions in the main are areas of granulomatous inflammation with the parasites within nerve



cells (Fig. 479), foci of softening, and gritty patches and streaks. The most remarkable feature, both in children and adults, is the presence of calcification which may be extreme in degree and visible radiologically.

**WERNICKE'S DISEASE.**—This rare condition, known also as acute superior hemorrhagic polioencephalitis, is marked clinically by paralysis of the eye muscles, stupor or excitement, and usually death within a few days. The lesions are curiously restricted. The corpora mammillaria are constantly affected; in addition there may be lesions in the hypothalamus, thalamus, and periaqueductal gray matter. The gross lesions are congestion and hemorrhage. Death is not due to the lesions in the mammillary bodies, but to a profound disturbance of carbohydrate metabolism with accompanying hypoglycemia. The characteristic microscopic lesion is vacuolation and disintegration of the intercellular tissue with preservation of the nerve cells. It is as if these cells had remained intact in the center of an area of brain softening (Fig. 478). The condition presents a clear-cut pathological entity, but one which is easily overlooked at autopsy unless borne in mind. The hemorrhagic lesions in the walls of the third ventricle and aqueduct and the floor of the fourth ventricle are well brought out by Pickworth's benzidine stain, as is beautifully shown in Campbell and Biggart's paper. When Wernicke originally described the condition in 1881 he ascribed it to alcoholism, but it is now believed to be a deficiency disease, because similar lesions can be produced experimentally by vitamin B<sub>1</sub> deficiency. It is really cerebral beri-beri, and can be cured rapidly and completely in the early stages by injections of thiamin.

**DRUG ENCEPHALITIS.**—It has long been known that a hemorrhagic encephalitis may follow the use of arsphenamine compounds and the sulphonamide group in hypersensitive individuals. It would now appear that a similar form of encephalopathy may develop in the course of long-continued treatment with streptomycin and para-amino-salicylic acid (Cavanagh). The lesions take the form of areas of anemic necrosis in the cortex and subjacent white matter, with an intense microglial reaction and large numbers of foam cells filled with lipid. The basic vascular lesions are proliferation of the capillary endothelium, hyaline thrombi plugging these vessels, and ring hemorrhages. Similar lesions are seen in the arsphenamine and sulphonamide cases. It is probable that the attack falls on the hypersensitive vascular endothelium.

**Myelitis.**—Acute inflammation of the spinal cord is rather rare. It may be *traumatic*, due to injury of the spine, or *infective*, due to septic embolism, to the infective fevers, or to syphilis. The *syphilitic* form is discussed in connection with syphilis of the nervous system. There is usually complete paralysis below the site of the lesion. This is usually in the lumbar region, so that the legs show a flaccid lower motor neurone paralysis with loss of deep reflexes and loss of sphincter control. There may be anesthesia below the lesion and hyperesthesia at the level of the lesion. If the lesion is in the cervical region both arms and legs will be paralyzed, but while the arms show a lower motor neurone paralysis, the legs develop an upper motor neurone type of paralysis, as the lower neurones remain intact.

**LESIONS.**—The inflammation is usually confined to one or at the most a few segments of the cord; this is called *transverse myelitis*, because the entire thickness of the cord is involved. Occasionally the inflammation may be diffused throughout the cord; this is *disseminated myelitis*. The affected part is soft and flattened, the distinction between gray and white matter is lost, and liquefaction may occur. *Microscopically* there is great



destruction of nerve cells and nerve fibers, of gray and white matter. Among the débris are large numbers of scavenger cells derived from the microglia. Perivascular collections of inflammatory cells are present in the surrounding tissue. The degeneration of the nerve fibers can be demonstrated in early cases by Marchi's method and in old cases by the Weigert myelin sheath stain.

**LANDRY'S PARALYSIS.**—This very rare disease is an acute ascending paralysis, in which first the legs, then the arms, and finally the intercostal muscles and diaphragm are paralyzed, with death from respiratory failure. Sometimes the paralysis is descending instead of ascending. The pathological changes are remarkably slight, for death usually occurs in three or four days. There is degeneration of the motor cells of the spinal cord and breaking up of the medullary sheaths of the corresponding nerve fibers. There are no perivascular collars of cells. The mode of progression suggests a virus disease.

## SYPHILIS OF THE NERVOUS SYSTEM

Syphilis of the nervous system used to be a matter of the greatest importance and much space was devoted to it in these pages. Chemotherapy has changed the picture completely, and the account of the pathological changes has been correspondingly curtailed. The lesions may take four forms: gumma, meningoencephalitis, tabes dorsalis and general paresis.

**Gumma.**—A gumma is a firm gray mass usually arising from the meninges and extending into the brain, producing the clinical picture of a cerebral tumor. It is almost never seen now.

**Syphilitic Meningoencephalitis.**—This is a diffuse inflammation of the meninges extending into the brain. It is most marked at the base of the brain, and involves the cranial nerves, particularly the third, fourth and sixth, with accompanying ptosis, strabismus and diplopia. The perivascular sheaths are also filled with a similar exudate, and it is these which constitute the encephalitis. *Syphilitic myelitis* is a much more distinct entity than syphilitic encephalitis, and is indeed the commonest form of myelitis. It is of the transverse type, limited to a few segments. Thrombosis of the diseased vessels is probably a major etiological factor, as a result of which there is softening of the cord and marked destruction of nerve cells and fibers. *Syphilitic arteritis* is a marked feature of all the lesions. The adventitia is infiltrated with round cells and the intima is uniformly thickened. The result of this endarteritis obliterans is to produce great narrowing or actual closure of the lumen, which leads naturally to thrombosis. Aneurism formation is not a result of cerebral syphilis, for the diffuse thickening does not weaken the vessel as do the patchy lesions of syphilitic aortitis. There may be a gummatous process around the vessel, a gummatous arteritis.

**CEREBROSPINAL FLUID.**—In acute syphilitic meningitis the reaction is severe and there is often a lymphocytosis of 500 or more. This high cell count is very suggestive of syphilitic meningitis. The protein content is high, the Wassermann reaction is positive, and the colloidal gold curve may be of the paretic or mid-zone types. A gumma causes much slighter changes, the Wassermann and colloidal gold

reactions are weak or negative, and the lymphocytosis and protein increase are slight. If the lesions are chiefly vascular, the fluid may be practically normal.

**Tabes Dorsalis.**—Tabes dorsalis or locomotor ataxia is a syphilitic disease of the cord, a late manifestation usually coming on from ten to fifteen years after the primary infection, although the interval may occasionally be as short as two years. The indirect evidence that the disease is syphilitic is conclusive, but spirochetes have very seldom indeed been found in the cord, nerve roots or ganglia, and the lesions bear no resemblance to the ordinary changes produced by syphilis.

**LESIONS.**—The true tabetic lesion is a degeneration and disappearance of the posterior columns of the cord and their replacement by neuroglial tissue. This lesion can be recognized with the naked eye. The pia over the dorsal columns is thickened and adherent. The surface of these columns



FIG. 480.—Tabes dorsalis: degeneration of posterior columns. (Weigert's myelin sheath stain.)

is no longer convex, but flattened or concave, and on the cut surface they are gray and translucent so that they stand out clearly from the rest of the white matter. It is the wasting of the dorsal columns which gives the disease its name (*tabes*, wasting). The posterior nerve roots are atrophied and shrivelled in comparison with the plump anterior roots, but this distinction is not so easy to recognize.

The *microscopic change* is seen in sections stained with Weigert's myelin sheath stain or the simpler iron hematoxylin. The normal white matter is stained black, but the degenerated posterior columns remain unstained (Fig. 480). The lesions are usually most marked in the lumbar region, but in the so-called cervical tabes they are confined to the cervical region. The first change is a demyelination, and droplets of myelin can be demonstrated by the Marchi method or Scharlach R. The axis cylinders become

disintegrated, and in time the whole of the medullary sheath disappears. There is proliferation of astrocytes and a replacement gliosis.

**THE RELATION OF SYMPTOMS TO LESIONS.**—*Sensory disturbances* include parasthesias, pain, and loss of muscle and vibration sense. The patient feels as if he were walking on something soft like cotton wool. "Lightning pains" of extreme severity shoot down the legs. The first effect of the lesion seems to be to set up violent impulses in the pain sensibility fibers and in the posterior nerve roots. There is also objective disturbance of pain sensibility in the shape of analgesia of the back and legs, so that the pain of lumbar puncture is not felt. The pain fibers end at once in the posterior horn of gray matter, and the second relay of fibers does not pass up in the posterior columns, from which it is evident that the interference must be in the posterior roots, not in the spinal cord. There is loss of muscle sense or sense of position, so that when the eyes are shut the position of the foot is unknown, and the patient sways when standing (Rombergism). The vibration sense is lost, so that he cannot feel the vibration of a tuning-fork placed on the shin. As both muscle sense and vibration sense impulses pass up in the posterior columns, it is natural that they should be lost.

*Incoordination* is due to interference with the muscle sense. As the patient is not sure of the position of his feet, he walks unsteadily and with a wide base (locomotor ataxia), lifting his feet high and throwing them down forcibly (stamping gait). *Loss of deep reflexes* in the legs is due to interference with the short fibers which anastomose directly around the cells of the anterior horn. The reflex arc is thus broken and the deep reflexes lost. The knee-jerk depends on the integrity of the third and fourth lumbar segments, and the Achilles jerk on the fifth lumbar and first sacral. In very low lesions the knee-jerk is preserved but the Achilles jerk is lost. The *light reflex* in the pupil is commonly lost, though contraction on accommodation is retained (Argyll-Robertson pupil). The nerve center for the pupillary reflex is the oculomotor nucleus in the midbrain, but the lesion is in the subependymal region of the aqueduct of Sylvius. In *optic atrophy* the optic nerve shows the same kind of lesion as the posterior nerve roots, but the way in which the lesion is produced is uncertain. The *visceral crises* are severe paroxysms of pain referred to various viscera (gastric, laryngeal, etc.). The cause is not known. The *trophic disturbances* are the most difficult to explain. The best known are Charcot's joint (a painless disorganization of one of the large joints), and the painless perforating ulcer of the foot. Possibly the analgesia which allows the parts to be severely traumatized may be more responsible than any loss of trophic nerve impulses.

**CEREBROSPINAL FLUID.**—There is lymphocytosis of from 10 to 50. In tabetic crises, possibly attended by meningeal irritation, there may be hundreds of cells with many polymorphonuclears. The protein is slightly increased. The colloidal gold curve is of the luetic type. The Wassermann reaction is positive in about 70 per cent of cases. In an old case of many years' duration the fluid may be practically normal.

**General Paresis.**—This disease, also known as general paralysis of the insane and dementia paralytica, is the most fearful of all the results of syphilitic infection. The lesions are the direct result of the action of the spirochetes, for the latter can be demonstrated in the cerebral cortex. The symptoms appear from ten to fifteen years after the primary infection. Similarly the juvenile form due to congenital syphilis appears about the age of ten years.

**SYMPTOMS.**—The name dementia paralytica describes the disease fairly well, because there is a general motor weakness, and if left to itself the condition pro-

gresses remorselessly to complete dementia. The mental disorder first affects the faculties of judgment, reason, self-control, and there is an accompanying loss of moral sense. As Oppenheim says, the work of deterioration begins first in the higher life of the mind and soul. As the dementia increases, the mental structure crumbles to the ground. Delusions of grandeur lead to a remarkable euphoria which contrasts strangely with the sad reality. The last stage is one of complete dementia. Tremors of the face, lips, and tongue are common. The speech is thick and characteristically slurring. The pupillary reflex is of the Argyll-Robertson type, with loss of reaction to light, but not to accommodation. Peculiar epileptiform or apoplectiform seizures ("paralytic seizures") may occur in which loss of consciousness may be followed by transient monoplegia or hemiplegia. Weakness of the muscles (paresis) is a constant feature of the disease, but never absolute paralysis.



FIG. 481.—Perivascular cuffing in general paresis.  $\times 85$ .

**LESIONS.**—The skull cap is thick, and there may be subdural hemorrhage with the formation of a thick membrane (pachymeningitis hæmorrhagica). The brain is small, with marked atrophy in the fronto-parietal region. The convolutions are wasted, the sulci widened, and there is a great compensatory excess of cerebrospinal fluid. The pia is thickened and adherent over the frontal lobe, so that when it is stripped off there is tearing or "decortication" of the surface. The lateral ventricles show a compensatory dilatation. The floor of the fourth ventricle is finely granular, giving it a frosted appearance, and the lateral ventricles may show the same condition to a lesser degree.

The *microscopic picture* is a mixture of syphilitic inflammation and

tissue downfall. The meninges are densely infiltrated with lymphocytes and plasma cells. (1) The *inflammatory lesions*, which are most marked in the cerebral cortex and the floor of the fourth ventricle, consist of dense perivascular collections of lymphocytes and plasma cells, the latter being especially numerous and characteristic (Fig. 481). These lesions are found throughout the entire thickness of the cortex. There may also be a diffuse infiltration of inflammatory cells. These lesions are to be attributed to the irritation produced by the spirochetes.

(2) The *degenerative lesions* are quite as marked, but they are more difficult to recognize unless one happens to be an expert neuropathologist. The general architecture of the cortex is completely lost, and the different layers can no longer be made out. There is a great outfall of cells, especially in the frontal and parietal regions. Most of the pyramidal cells may have disappeared. Those which remain show every degree of degeneration.

(3) *Neuroglial proliferation* is marked, especially in the superficial layer of the cortex and in the walls and floor of the ventricles. The astrocytes multiply and form a dense feltwork of fibers. These are responsible for the pial adhesions and the decortication. In the floor of the fourth ventricle the glial proliferation causes an irregular heaping up of the floor (Fig. 482). This is the cause of the granularity already described. The granulations are covered by ependyma, but some of the summits may be

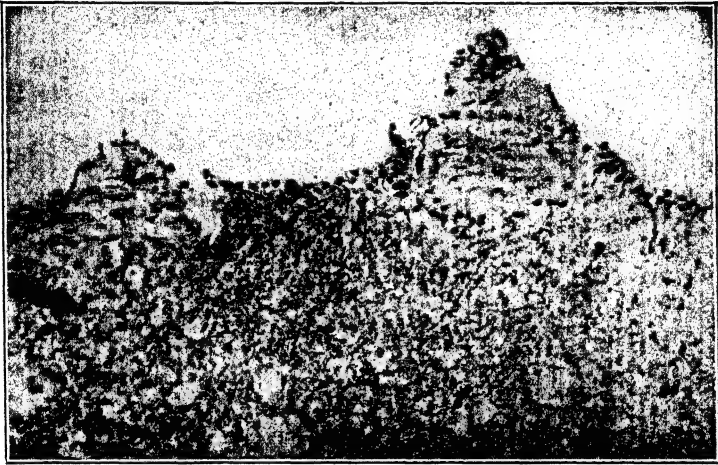


FIG. 482.—Granular floor of fourth ventricle in general paresis. The ependyma is desquamated from the mounds of neuroglia.  $\times 175$ .

bare. The microglia also proliferate, giving rise to large numbers of "rod cells" (Fig. 483), which form an intermediary stage between the microglial cell and the compound granular corpuscle. In sections of the cerebral and cerebellar cortex and of the basal ganglia the Prussian blue reaction shows iron-containing pigment in the cytoplasm of these cells and in perivascular spaces. The combination of the proliferation of "rod cells" and the presence of iron pigment in their cytoplasm is considered by Stern to be pathognomonic of general paresis.

**CEREBROSPINAL FLUID.**—The cells number from 30 to 100, and polymorphonuclears are often present, especially during convulsive seizures. The protein is increased. The Wassermann reaction



FIG. 483.—Rod cells.  $\times 300$ . (Silver carbonate stain.)

is positive and intense in from 96 to 100 per cent of untreated cases. The colloidal gold reaction gives a paretic curve.

### DISSEMINATED SCLEROSIS

This condition, also known as multiple sclerosis, is a chronic disease of the nervous system, characterized by curious remissions and relapses, and by the presence of multiple patches of sclerosis scattered diffusely throughout the gray and white matter of the brain and spinal cord. The incidence varies greatly in different countries. It is commonest in Switzerland, quite common in England, France, and Germany, fairly common in Canada and the United States, rare in South America, and unknown in China and Japan. The *cause* is unknown, but is almost certainly in infection. The lesions are very similar to, indeed identical with, those of acute infectious encephalomyelitis, especially post-vaccinal encephalitis, and it is more than possible that disseminated sclerosis is also caused by a filter-passing virus.

**SYMPTOMS.**—The patient, usually between the age of fifteen and thirty-five years, suffers from a great variety of sensory and motor disturbances, many of which are curiously and characteristically fleeting. There are paresthesias of various kinds in the hands and feet, spastic paralysis of the upper motor neurone type with exaggerated deep reflexes and a positive Babinski sign, loss of the abdominal reflex, and transient disturbance of the organic reflexes. The well-known *Charcot triad* of nystagmus, intention tremor, and staccato speech are late manifestations of incoördination. The cranial nerves may be affected, causing sudden blindness, pallor of the temporal side of each optic disc, and oculomotor palsies. The patient is absurdly cheerful, considering the progressive and incurable nature of his ailment. Although progressive, the most remarkable remissions often occur, during which most of the symptoms may disappear.

**LESIONS.**—The lesions are scattered widely through the white matter of the brain and cord, and can be seen and felt in the fresh specimen as well-defined gray translucent patches. The lesions are very numerous in the brain, being especially well marked in the pons, medulla, and cerebellar peduncles. There are patches in the optic nerve and optic chiasma. In the cord the lesions are most marked in the lateral columns (pyramidal tracts), but they are also present in the posterior columns.

The *microscopic picture* varies with the stage of the disease. Disseminated sclerosis is an inflammation with subsequent demyelination and gliosis. If the autopsy is done during the *early stage*, which is seldom possible, the medullary sheaths are found to be breaking up into droplets of myelin which can be stained with fat stains (osmic acid, Scharlach R), and the vessels are surrounded by collars of cells. Some of these cells are true inflammatory cells (lymphocytes and plasma cells), but others are compound granular corpuscles filled with droplets of myelin. It would appear, therefore, that the condition is inflammatory in nature, with demyelination as the chief result. The lesions are very similar to those of postvaccinal encephalitis, but in disseminated sclerosis the production of the lesions is a much more gradual process. In the *advanced stage*, the stage usually seen at autopsy, there are multiple neuroglial scars surrounding the blood

vessels, chiefly in the white matter and to a lesser extent in the gray matter. In Weigert-Pal sections the scarred areas appear white on a black background (Fig. 484). In these patches of sclerosis the axis cylinders may be wonderfully intact, thus accounting for the remarkable remissions of symptoms which may take place. Some of the axis cylinders degenerate and others disappear entirely. The astrocytes proliferate and the nerve fibers are replaced by a dense glial network. There is a remarkable absence of secondary degeneration above and below the lesions, so that the patches of degeneration remain isolated. In this respect the disease differs entirely from tabes which is a system degeneration, *i. e.*, a condition affecting an entire system of fibers. Evidence of inflammation such as perivascular collars of cells is entirely lacking in the late stages of the disease.



FIG. 484.—Multiple sclerosis. There are irregular asymmetrical patches of degeneration in the posterior and lateral columns. (Weigert's myelin stain.)  $\times 8$ .

**THE RELATION OF SYMPTOMS TO LESIONS.**—The lesions are much more widespread than the severity of the symptoms would suggest. "Sclerosis creates multa, but not multum," as Oppenheim puts it. The comparative integrity of the axis cylinders explains the unexpected way in which such serious symptoms as paralysis or loss of vision may suddenly clear up. Lesions in the pyramidal tracts at different levels are responsible for the spastic paraplegia, exaggerated deep reflexes, and positive Babinski sign. The sensory changes are due to the lesions in the posterior columns. The absence of muscular atrophy and reaction of degeneration is to be expected from the fact that the anterior horns escape serious injury. The cerebellar incoördination, evidenced by nystagmus, intention tremor and scanning speech, is caused by lesions in the cerebellar peduncles which cut off the coördinating influences which play on the motor centers in the mid-brain and pons. The temporary loss of vision and the pallor of the temporal side of the discs are due to lesions of the optic chiasma or optic nerve. Diplopia, strabismus, and ptosis are caused by patches of sclerosis in the mid-brain.



**CEREBROSPINAL FLUID.**—With one exception this shows little change. There is a mild lymphocytosis in the early cases and a slight increase of protein, but in the advanced sclerotic stage these changes are absent. The exception is the colloidal gold reaction, which in about one-half the cases gives a paretic curve, though the Wassermann reaction is always normal.

**ENCEPHALITIS PERIAXIALIS DIFFUSA. SCHILDER'S DISEASE.**—This rare condition, which affects children and young adults, closely resembles disseminated sclerosis in its pathology, but it involves the cerebral hemispheres, not the brain stem and spinal cord. The disease is essentially a demyelination of the white matter of both hemispheres, the gray matter escaping untouched. The affected areas are soft and gelatinous, gray and translucent. The process usually starts in the occipital lobes and spreads forward, but it may begin in any part of the cerebrum. The *microscopic features* are similar to those of early disseminated sclerosis and postvaccinal encephalitis, *i.e.*, demyelination with destruction of the axis cylinders, perivascular collars of scavenger cells, and early gliosis. There is marked secondary degeneration of the affected paths. The cause of the condition is unknown.

The onset is acute and the course rapidly progressive but some cases may recover. The symptoms correspond with the lesions to a degree never seen in disseminated sclerosis. There is early blindness of cerebral type (occipital lobe), deafness (temporal lobe), sensory disturbances and loss of sense of position (parietal lobe), spastic paralysis (motor area), and mental deterioration (frontal lobe). Convulsions are common. The combination in a child of progressive blindness, progressive spastic paralysis, and progressive mental failure is pathognomonic.

Resembling this condition is "*Swayback*," a congenital demyelinating disease of lambs, characterized by incoördination of movement, tremors of the head, blindness, and spastic paralysis. There may be demyelination of an entire cerebral hemisphere. In some flocks as many as 90 per cent of the lambs born are affected.

## CHRONIC MOTOR NEURONE DEGENERATION

Three different clinical entities, all of them rare, may be grouped under this heading, for in all of them the underlying basis is a primary degeneration of the motor neurones, upper or lower or both. They are all variants of one pathological process. In *progressive muscular atrophy* the lesion is in the anterior horn, in *bulbar palsy* it is in the bulbar centers, and in *amyotrophic lateral sclerosis* both the upper and lower motor neurones degenerate. There is no involvement of the sensory side. The cause of the condition is unknown and its nature uncertain. It occurs in persons over middle age, there is nothing inflammatory about it, and it seems to be a pure degeneration, a gradual neuronal decay, an abiotrophy. It is possible that a food deficiency, vitamin or otherwise, may be responsible. In all three forms there is progressive muscular weakness with atrophy and fibrillary tremors in the affected muscles.

1. **AMYOTROPHIC LATERAL SCLEROSIS.**—Both the upper and lower motor neurones are involved. There is atrophy of the anterior horns in the cord with great disappearance of the motor cells and wasting of the anterior nerve roots; the condition of the nerve roots should be compared with what is found in tabes. The remaining anterior horn cells show every degree of degeneration. The pyramidal tracts are degenerated, and there is corresponding degeneration of the large Betz cells in the motor cortex. Late in the disease the motor nuclei in the pons and me-



dulla degenerate. There is marked atrophy of the affected muscles. The change is spotty, not diffuse, many of the fibers being comparatively intact. These are innervated by the nerve cells which have escaped destruction. There is a replacement fibrosis.

The chief symptoms are weakness, wasting, and fibrillary tremors of the muscles. The amyotrophy begins in the small muscles of the hands (thenar, hypothenar and interossei), and spreads to the forearm and shoulder. Spasticity of the legs, exaggerated deep reflexes and a positive Babinski sign due to an upper motor neurone lesion may appear even earlier. Symptoms of bulbar paralysis (see below) complete the picture at the end. The patient seldom survives more than three years, death being due to bulbar paralysis.

2. PROGRESSIVE MUSCULAR ATROPHY.—This is amyotrophic lateral sclerosis without clinical evidence of an upper motor neurone lesion, although at autopsy the lateral columns may show some degeneration. The disease is much rarer than the preceding form. The fibrillary tremors form the most striking feature of the clinical picture. As the bulbar centers are spared, the patient may drag out an existence for many years.

3. PROGRESSIVE BULBAR PALSY.—The condition may be purely bulbar, or may be the end-stage of an amyotrophic lateral sclerosis. The motor nuclei of the pons and medulla are involved, *i.e.*, the seventh, ninth, tenth, eleventh and twelfth nerves. The clinical picture is best described by the alternative name, glosso-labio-pharyngeal paralysis. The first symptom is difficulty in articulation with loss of the labials. Owing to the weakness of the lips they are at first held in a peculiarly stiff manner; after a time the mouth remains permanently open. The tongue wastes and shows marked fibrillary tremors. There is paralysis of the palate and the pharynx, so that swallowing becomes impossible. The upper part of the face escapes.

LITTLE'S DISEASE.—The condition of *congenital spastic diplegia* is due to an upper motor neurone degeneration, or rather to an *agenesia* or failure of development on the part of the motor cortical cells and the pyramidal tracts. The convolutions in the motor area are small and atrophic (*microgyria*). There is an association with premature birth, but this is not a causal factor. The symptoms usually appear about a year after birth. The picture is purely motor. The child walks with a "cross-legged" or "scissors" gait, with great spasticity of the legs. The deep reflexes are exaggerated and there is a double Babinski sign. There may be slight involvement of the arms.

SPASTIC CEREBRAL PARALYSIS.—Spastic cerebral paralysis or birth palsy is quite a different condition from Little's disease, and is due to a meningeal hemorrhage at the time of birth. A monoplegia or hemiplegia is commoner than diplegia, and the paralysis is evident soon after birth. A gross lesion is always present.

PICK'S CONVOLUTIONAL ATROPHY.—This is a very rare form of *agenesia* which manifests itself in the presenile period (fifty to sixty years). The brain is shrunken, and shows extreme symmetrical localized atrophy of parts of the cerebrum. The change is most marked in the frontal region, but in a case of the writer's the occipital convolutions were also extremely small. The atrophy is not arteriosclerotic or senile in character. The condition is progressive, and is accompanied by marked dementia. It is the phylogenetically younger parts of the brain which are most affected.

ALZHEIMER'S DISEASE.—In this presenile condition the distinctive microscopic features of the atrophic brain are senile plaques and neurofibrillary changes. The plaques consist of an acellular argyrophilic center surrounded by distorted neuroglial and nerve fibers. The neurofibrils become thickened, fragmented, and finally disintegrate. With the periodic acid-Schiff stain the senile plaques are seen to consist of amorphous as well as cellular and fibrillary elements (Margolis). The

amorphous material is PAS-positive, whereas the other elements are PAS-negative. The plaques seem to be the result of the deposition of colloids in the ground substance of the cortex, the cellular components being probably reacting glial cells.

### SUBACUTE COMBINED DEGENERATION OF THE CORD

This nervous disease, characterized by paresthesias of the hands and feet and spastic paralysis of the legs, is closely related to pernicious anemia. Nearly every case sooner or later develops a macrocytic hyperchromic type of anemia, even though there may not be a full-fledged blood picture of pernicious anemia. In rare cases combined degeneration may complicate other conditions, such as leukemia and cancer of the stomach. The cord lesions are not due to the anemia, for nervous symptoms may develop

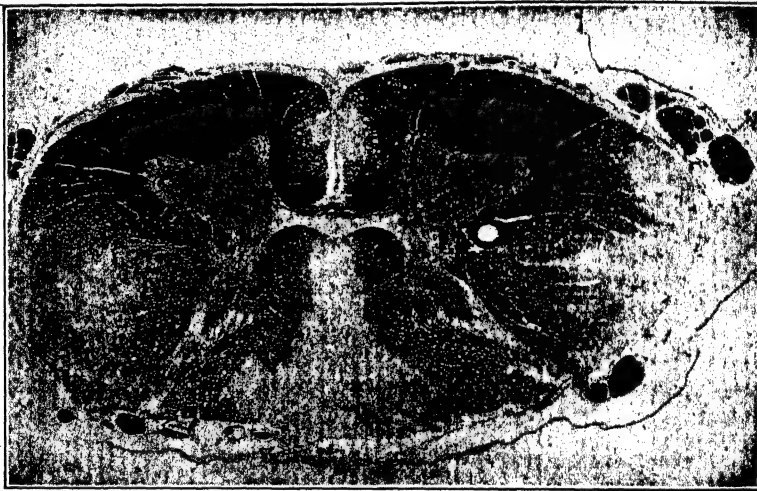


FIG. 485.—Subacute combined degeneration of the cord. Marked degeneration in the posterior columns, the crossed pyramidal and direct pyramidal tracts, and the right indirect cerebellar tract. (Weigert's myelin stain.)  $\times 8$ .

long before there is any sign of anemia. They are due either to the deficiency responsible for the bone-marrow lesions, or to some other deficiency.

**LESIONS.**—These are most marked in the mid-dorsal region, with ascending secondary degeneration in the cervical cord and descending secondary degeneration in the lumbar cord. The lesions are symmetrical, and involve the posterior columns, crossed and direct pyramidal tracts, and the cerebellar tracts (Fig. 485). In the early stage and in remissions they are confined to the dorsal columns. They can be seen as translucent patches with the naked eye. It is not a system disease; the lesions are formed by the fusion of many small patches. There is first demyelination with complete destruction of the medullary sheaths, followed later by disappearance of the axis cylinders. In the more recent lesions there is a complete absence of neuroglial proliferation, but in old lesions there may be some degree of secondary gliosis.

**THE RELATION OF SYMPTOMS TO LESIONS.**—There is exact correspondence between the lesions and symptoms. The earliest symptom is numbness and tingling at the tips of the fingers and toes, a feeling of "pins and needles." Later there may be sensory loss, ataxia, and loss of the sense of position. The knee-jerks may be lost. All of these are posterior column symptoms. In other cases there are lateral column symptoms, *i.e.*, spastic paralysis, exaggerated deep reflexes, and a double Babinski sign. The end-stage is one of flaccid paralysis with complete sensory loss and paralysis of the sphincters; this corresponds with disappearance of all the long tracts in the dorsal region.

### FRIEDREICH'S ATAXIA

This rare familial disease belongs to the group of the abiotrophies, in which slow degeneration of several of the tracts of the nervous system occurs without any obvious reason. It is a disease of the young. The distribution of the lesions resembles that in subacute combined degeneration, for the disease is a combined degeneration affecting both posterior and lateral columns (Fig. 486). Owing to the lesions in the posterior columns there is loss of the deep reflexes and of deep muscle sense, the latter partially accounting for the ataxia, which affects the arms as well as the legs. But there is a large cerebellar element in the ataxia ("cerebellar reel"), due to involvement of the direct cerebellar tract. Lesions in the pyramidal tracts cause muscular weakness and a positive Babinski sign, even though the knee-jerks are lost. A characteristic deformity of the foot (high arch and hammer toe) and scoliosis are probably due to the pyramidal tract degeneration causing asymmetrical weakness of the muscles during the period of growth. Nystagmus and scanning speech are characteristic features, but their method of production is not obvious. Although posterior column sclerosis is present in both of the spinal ataxias (Friedreich's and locomotor), the former presents none of the lightning pains and other sensory disturbances which are so characteristic of tabes, a significant fact which suggests that the cause of these disturbances should be looked for outside the spinal cord.

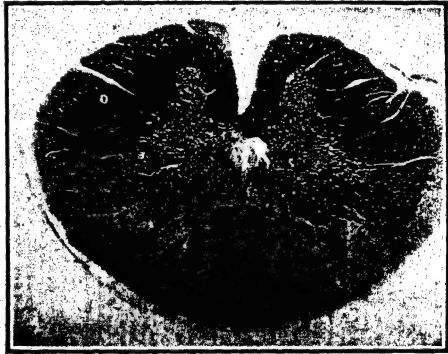


Fig. 486.—Friedreich's ataxia.  $\times 7$ .

### SYRINGOMYELIA

This is another rare disease of the earlier part of life depending on a perversion of development. It is therefore often associated with spina bifida and other congenital anomalies. The outstanding symptoms are dissociated anesthesia (loss of sensibility to pain and temperature with preservation of touch), muscular atrophy in the arms, a spastic condition of the legs, and certain so-called trophic lesions.

**LESIONS.**—The essential lesion is a gliosis in the gray commissure and the base of the posterior horns in the lower cervical and upper dorsal region. This new-formed glial tissue becomes softened and liquefied so that a tubular cavity is formed (*syrinx*, a tube, the same word as syringe) (Fig. 487). The process may extend

through the entire length of the cord, and even up into the brain stem. The cavity is separate from the central canals of the cord. The affected part is large, soft and flattened. The cavity is often lined by a layer of ependyma. It should be remembered that ependymal cells are merely specialized neuroglial cells, and that they may proliferate, giving rise to a gliosis, just as they may form an ependymal glioma. In the latter tumor the cells tend to surround tiny cavities, and it is possible that a similar tendency may explain the cavity formation in syringomyelia. All this is very theoretical, but there is nothing better to put in its place. We may regard the process, then, as a benign neoplasia of glial tissue, in which ependymal cells possibly play a prominent part.

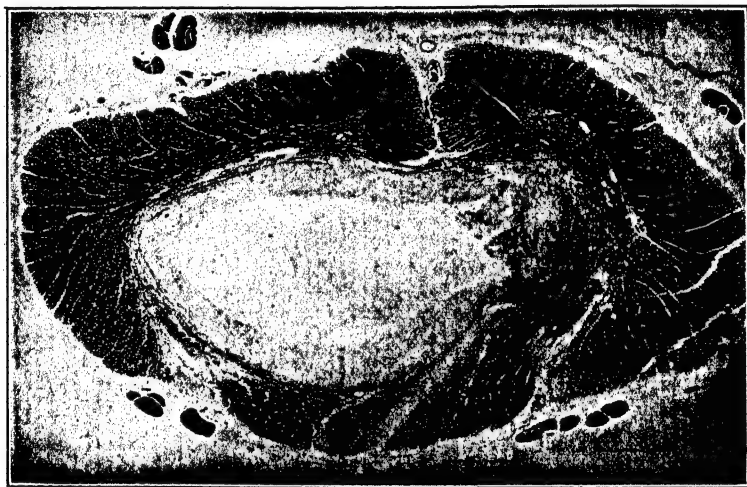


FIG. 487.—Syringomyelia. Marked cavity formation in the center of the cord, with surrounding zone of gliosis. (Weigert's myelin stain.)  $\times 8$ .

**THE RELATION OF SYMPTOMS TO LESIONS.**—The *dissociated anesthesia* is observed in the arms, as the lesion is commonly in the cervical cord. The fibers for pain and temperature cross in the gray commissure, and are therefore caught in the destructive process. Most of the touch fibers pass up in the posterior columns of the same side and therefore escape. This explains the dissociation of the anesthesia. *Spasticity* of the legs with some loss of power is due to pressure on the pyramidal tracts in the cervical region. In the arms there is *muscular atrophy* of the lower motor neurone type, similar to that seen in progressive muscular atrophy. As the pathological process seldom involves the anterior horns, the reason for this atrophy is obscure. The *trophic lesions* are still more obscure. The name is unfortunate, for it is probable that the root of the trouble is not the cutting off of hypothetical trophic influences from the cord, but the anesthesia which permits the tissues to be unduly traumatized. Thus burns on the hands are of common occurrence, as the patient is insensitive to heat. The best known example is the *Charcot joint*, usually the shoulder or elbow. Its chief characteristic is its extreme painlessness, although the joint is completely disorganized and may become dislocated. Such an insensitive joint must receive much trauma against which there is now no protective mechanism, and this may lead to the remarkable disintegration characteristic of the condition.

**HYDROMYELIA.**—This is a simple dilatation of the central canal of the cord. It may affect the whole or only part of the canals. It may be associated with hydrocephalus, and is related to that condition rather than to syringomyelia.

## DISEASES OF THE CORPUS STRIATUM

In some diseases the lesions are confined to the corpus striatum, in others the chief changes affect this area. The main effects of disease are rigidity, tremor and disorders of movement. Diseases in which these features are prominent are Parkinson's disease, progressive lenticular degeneration, Huntington's chorea and Sydenham's chorea.

**Paralysis Agitans.**—Parkinson's disease ("the shaking palsy") is a perfect example of disease of the extrapyramidal system, and will therefore be described in some detail. The clinical picture was drawn more than a hundred years ago by Parkinson with the hand of a master. The classical triad of symptoms are rigidity, tremor, and an attitude of flexion. (1) The *rigidity* results in a general absence of motor activity; there are none of the little movements depending on a healthy corpus striatum. It involves all the voluntary muscles, until at last the unhappy sufferer becomes as rigid as a block of marble. Articulation and swallowing become difficult, and finally there is complete anarthria and extreme dysphagia. The rigidity gives the face the familiar Parkinsonian mask. The mouth cannot be closed and the saliva drools down the chin. (2) The *tremor* affects the fingers and hands, giving a cigarette-rolling movement. It is present when the part is at rest, disappearing for a few minutes with movement. To use Parkinson's own words: "Commencing in one arm the wearisome agitation is borne until beyond sufferance, when by sudden changing of the posture it is for a time stopped in that limb." It is dependent on the integrity of the pyramidal tract for it disappears in a limb paralyzed as the result of a stroke, only to reappear as the power returns. (3) The whole attitude is one of *flexion*. The head is flexed on the chest, the body is bowed, the arms and wrist are flexed, the knees are bent. As the center of gravity is thrown forward he has to walk on the forepart of the feet, and comes to assume an overhanging position. "He is irresistibly impelled to take much quicker and shorter steps, and thereby to adopt unwillingly a running pace." An advanced example of the disease can be diagnosed at a glance.

**LESIONS.**—The lesions take the form of degenerative changes in the corpus striatum, especially disappearance of the large motor cells of the globus pallidus. More than this it is not possible to say. The changes are not confined to the globus pallidus, so that it is not justifiable to regard the condition as a pure syndrome of the globus pallidus. The cause of the degeneration is not known; possibly it is in the nature of a senile atrophy. Edema, degeneration, and fibrosis have been described in the muscle spindles (neuromuscular bundles) of the small muscles of the thumb. The rigidity and tremor are evidently the result of the lesions in the corpus striatum.

The possibility of a relation to trauma has been a matter of much dispute. Undoubtedly severe injury to the head may be followed after a latent interval by the appearance of tremors, due probably to destructive lesions in the basal ganglia

caused by a wave of cerebrospinal fluid set up by the blow. These post-traumatic cases, however, do not present all the features of Parkinson's disease, and they may occur at a much earlier age.

**POST-ENCEPHALITIC PARALYSIS AGITANS.**—This condition, commonly called post-encephalitic Parkinsonism, presents the same clinical picture as that which has just been described, but the course is usually not progressive. In spite of this similarity it is not a corpus striatum disease, for the degenerative lesions are in the substantia nigra and the red nucleus. The pigmented cells of the former may largely disappear. It is therefore a disease of the extrapyramidal system.

**PROGRESSIVE LENTICULAR DEGENERATION.**—This rare condition is also called hepato-lenticular degeneration and Wilson's disease. It is familial, affects young people, and is progressively fatal. The chief *clinical features* are muscular rigidity, tremor of the Parkinson type, difficulty with articulation, and marked emotion-alism. There are always two entirely different *lesions*, as indicated by the name hepato-lenticular degeneration. The *first* is a degeneration of the lenticular nucleus, which may go on to softening and cavity formation. It is a pure striatal lesion, involving the caudate as well as the lenticular nucleus, but leaving the thalamus untouched. There is a greenish pigmentation along the margin of the cornea. The *second* lesion is a cirrhosis of the liver of the Laennec type. It is possible that an inherited error in copper metabolism may be responsible for the lesions both in the liver and the brain (Denny-Brown and Porter). The copper content of these organs may be 10 times that of the normal. The Kayser-Fleischer rings consist of copper, and there may be sun-flower cataract due to copper deposits on the surface of the lens. The brown pigmentation of the lenticular nucleus is probably due to an accumulation of copper. Cirrhosis of the liver can be produced in the experimental animal by the administration of copper. The chief route of normal excretion of copper is the bile, and in Wilson's disease there is an excessive output of copper and urine. It may well be that the basic trouble is an overabsorption of copper from the bowel, just as in hemochromatosis there is believed to be an overabsorption of iron. It may be noted that when the liver of the experimental animal is damaged by ligation of the hepatic artery or is by-passed by means of an Eck fistula, severe cerebral damage results (Baker). Moreover, cirrhosis and other degenerative diseases of the liver in man may be associated with necrotic foci in the corpus striatum apart from Wilson's disease. Cirrhosis and other degenerative diseases of the liver in man may be associated with necrotic foci in the corpus striatum.

**HUNTINGTON'S CHOREA.**—This rare disease has an extremely marked hereditary tendency, but does not appear until middle life. The two chief *symptoms* are involuntary movements and tremors of choreiform character, and mental deterioration going on to dementia. Two *lesions* have been described: (1) atrophy of the cortical nerve cells and their associated fibers; (2) destruction and disappearance of the cells of the putamen and caudate nucleus (neostriatum) with comparative escape of the globus pallidus. The mental deterioration is evidently due to the extensive cortical changes, and the choreiform movements may be attributed to the loss of controlling influences from the neostriatum.

**SYDENHAM'S CHOREA.**—St. Vitus' dance is one of the commonest of nervous disorders, yet its pathology is still obscure. It usually occurs in girls, and nearly always before the age of twenty years. Chorea is a manifestation of rheumatic fever, but it may not be preceded by a definite arthritis, for rheumatic manifestations in childhood are not necessarily arthritic. The *symptoms* take the form of sudden, irregular, involuntary movements. The disease runs its course in a few weeks and rarely ends in death. The *lesions* in the fatal cases are remarkably insignificant. There is marked hyperemia, a moderate perivascular lymphocytosis,

and slight degeneration of nerve cells. These changes are most marked in the cerebral cortex and the basal ganglia, especially the neostriatum.

### THE MUSCULAR DYSTROPHIES

The muscular dystrophies have several clinical divisions, but the basic pathology is the same. The disease begins in childhood, shows a very marked familial tendency so that several children in the family may be affected, attacks only the males, but is transmitted only by the females. The large muscles concerned with fixation (shoulder girdle, hip) are chiefly affected, the small muscles concerned with active movement (hand, etc.) usually escaping. This is the opposite to what occurs in progressive muscular atrophy. The largest group is known as *pseudohypertrophic muscular*



FIG. 488.—Pseudohypertrophic muscular dystrophy. The muscle fibers are swollen and are largely replaced by fat.  $\times 140$ .

*paralysis* because of a remarkable enlargement of the muscles of the calf or shoulder girdle. Although the muscles are enlarged, they are without power (all is not gold that glitters). The great symptom is muscular weakness. Owing to paralysis of the gluteal muscles the patient cannot rise from the floor in the usual way, but has to "climb up his legs." The muscles of the shoulder girdle may be principally affected (*facio-scapulo-humeral type*).

**LESIONS.**—These involve the muscles and interstitial tissue. In the common pseudohypertrophic form the muscles are large and firm; the gastrocnemius, deltoid, supraspinatus, and infraspinatus are most often affected. Other muscles are markedly atrophic. In the early stages the muscle fibers may be swollen, with loss of striations and increase of the



sarcolemma nuclei, but later the fibers become atrophic. In this stage there may be a marked increase of the interstitial tissue, and great deposits of fat may occur between the muscle fibers (Fig. 488). It is to these deposits of fat that most of the enlargement (pseudohypertrophy) is due. The exact cause of these deposits is not known, but indirect evidence suggests that they may be due to pituitary disturbance.

### INTRACRANIAL TUMORS

Tumors within the cranial cavity may be divided into two great groups, intracerebral and extracerebral. The intracerebral group comprise the gliomas, metastatic carcinoma, and a few miscellaneous tumors such as hemangioma. The extracerebral group, far more favorable from the surgical standpoint, comprise the meningiomas, acoustic neuromas, and tumors of the pituitary and craniopharyngiomas which have already been considered in connection with the pituitary body. All of these tumors may produce certain general effects, but these effects are most conveniently discussed with reference to the group of the gliomas.

**GENERAL EFFECTS.**—*Edema* is of common occurrence in the neighborhood of a brain tumor. Enlargement of the affected part, which is a constant accompaniment of tumor, may be largely due to the edema. *Secondary hydrocephalus* is perhaps the most important effect, for it is largely responsible for the increased intracranial pressure, and therefore for the classical (though late) symptoms of brain tumor, *i.e.*, headache, vomiting, and optic neuritis. Tumors in the posterior fossa are most likely to cause severe hydrocephalus, but a tumor in any position may produce some dilatation of the ventricles. A tumor in the posterior fossa may block the opening of the aqueduct of Sylvius or may press on the great vein of Galen as it curves around the splenium of the corpus callosum. The vein drains the choroid plexus, and pressure upon it leads to an increased production of cerebrospinal fluid and hydrocephalus. But a tumor in any part of the cranial cavity may cause hydrocephalus. This is probably due to pressure of the brain stem containing the narrow aqueduct of Sylvius against the hard edge of the tentorium cerebelli. *Distortion of the lateral ventricle* by the tumor is a common occurrence, and this can be detected by means of ventriculography, *i.e.*, filling the ventricles with air and taking a roentgen-ray picture. Displacement of a calcified pineal gland in the x-ray film is another indication of a space-occupying lesion. The *increased intracranial pressure* causes flattening of the convolutions and obliteration of the subarachnoid space. At operation the brain may not show the normal pulsation. The *optic neuritis* is due to the fluid in the subarachnoid space being forced into the lymph spaces in the sheath of the optic nerve; this interferes with the venous return, and the result is edema and hemorrhage which give the ophthalmoscopic picture of choked disc and optic neuritis. When the intracranial pressure is high, clusters of arachnoid cells may penetrate the dura and appear on its cranial surface as nodular outgrowths. *Hemorrhage* into a glioma is common, and may cause a sudden exacerbation of symptoms or even death. The *skull* may show a characteristic mottling like beaten silver in the roentgen-ray picture from pressure of the convolutions, due to increased intracranial pressure. In meningioma there may be an even more characteristic local hyperostosis of the overlying bone.

The *relation of trauma to glioma* is a matter on which there is no uniformity of opinion. Some of those who have examined the statistics most carefully are of the opinion that no such relationship exists. The difficulty is to distinguish between mere coincidence and true causal relationship.



**Glioma.**—For practical purposes nearly all the tumors of the brain are neoplasms of the interstitial tissue, *i. e.*, gliomas. Of the three varieties of interstitial tissue, the microglia never gives rise to tumors, and the oligodendroglia very seldom does, so that practically all the gliomas arise from the astrocytes. The various intracranial tumors may be divided into a clinically benign group of slow growth and a much more malignant group. To the more benign group belong meningioma, acoustic nerve tumor, pituitary adenoma, cerebellar astrocytoma, ependymoma, blood vessel tumors, and congenital tumors. The important members of the malignant group are glioblastoma, medulloblastoma and cerebral astrocytoma, although to a much less degree. It must be noted that although some of the gliomas are among the most malignant of tumors, they never give rise to metastases. If large celloidin sections of the entire tumor and the surrounding brain tissue are made it will be found that in about one-third of the cases the glioma is relatively circumscribed, the microscopic limits corresponding fairly closely with the visible limits. About 60 per cent are diffuse, with microscopic limits extending widely beyond the grossly visible limits (Scherer). This is true of all cerebral astrocytomas. There may be multicentric growth, but this is practically confined to the glioblastomas. About 30 per cent of gliomas are bilateral.

For many years the accepted classification of the gliomas has been that proposed by Bailey and Cushing in 1926. This was based on the assumed resemblance of the various cells in the gliomas to embryonic cells recognizable in the differentiation of the developing nervous system. Such terms as astrocytoma arising from astrocytes, astroblastoma from astroblasts, and spongioblastoma (now called glioblastoma) from spongioblasts. It is well known, however, that an intermingling of different types of cells can be found in the different tumors, which destroys the idea of specificity. Kernohan's concept that the cells in the more rapidly growing gliomas represent different phases of dedifferentiation rather than undifferentiation appears much more satisfying. Astrocytoma, astroblastoma and glioblastoma multiforme would then represent different degrees of malignancy of the same type of neoplasm. The four adult types of cells in the central nervous system are astrocytes, ependymal cells, oligodendroglial cells and nerve cells. Each of these, in that order of frequency, may give rise to tumors of varying degrees of anaplasia and malignancy.

In support of the view that the common forms of glioma are variations of one basic type is the observation of Zimmerman and Maier that all the usual varieties can be induced in mice by the intracerebral implantation of pellets of a chemical carcinogen such as methylcholanthrene. A single tumor may consist of astrocytic, spongioblastic and oligodendrocytic parts. By homologous subcutaneous transplantation of such mixed tumors it has been possible to establish pure lines of the individual neoplasms. From a single tumor it has been possible to develop an ependymoma, an astrocytoma, and an oligodendrogloma.

A peculiar feature of the gliomas is that, no matter how malignant they may be, they do not metastasize outside the central nervous system. They make up for this, however, by showing a tendency to seeding throughout the subarachnoid space, both cerebral and spinal, a tendency which is

much more marked in the case of the medulloblastoma. The reason why they do not metastasize appears to be that they do not invade the blood vessels, nor do the Virchow-Robin spaces communicate with the general lymphatic system. When the gliomas are implanted in the eye, the peritoneal cavity or the subcutaneous tissue they grow readily.

*Local effects* may show themselves as symptoms which suggest at an early date the presence and location of a brain tumor. Thus tumors of the frontal lobe are associated with deterioration of the personality, those of the temporal lobe with dreamy states and so-called uncinat fits characterized by unpleasant odors and a feeling of unreality, those of the occipital lobe with visual hallucinations such as scintillating lights. The onset of

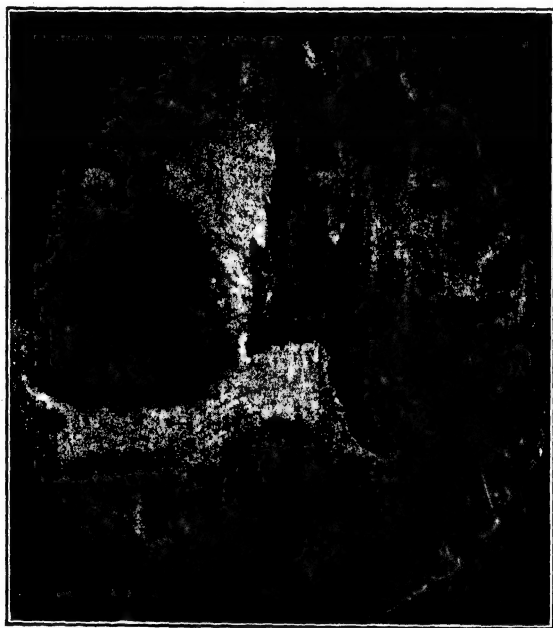


FIG. 489.—Glioblastoma showing hemorrhage in center.

symptoms may be sudden, such as a stroke due to hemorrhage in the tumor or to occlusion of a vessel and thrombosis, but the commonest sudden symptom in the adult is convulsions. The recognition of these early manifestations of cerebral tumor is of great importance. If one waits for the development of such classical signs as vomiting and optic neuritis it is too late for successful neurosurgery. It may be noted that most of the tumors in childhood occur in and around the cerebellum, and that one-third of these are benign.

**Glioblastoma Multiforme.**—This is the commonest and most malignant of the gliomas. It is a tumor of middle life, and is seldom found outside the cerebral hemispheres. It is not infrequently multiple—an unusual occurrence in a malignant tumor. If not treated, it rapidly kills the patient.

The tumor is soft, gray, ill-defined, vascular, and often shows evidence of degeneration such as necrosis, hemorrhage, and cyst formation. Degeneration of the central part often gives the tumor a false appearance of encapsulation (Fig. 489); in reality it is highly invasive, and the surgeon's great difficulty is to know where the tumor ends and normal brain begins.

The *microscopic appearance* is characteristically varied. The tumor is highly cellular, and the cells are very pleomorphic, varying greatly in size and shape, recalling the varied cytological picture in osteogenic sarcoma of bone. This pleomorphism justifies the name "multiforme," which is applied to the common form of glioblastoma, in contrast to a rarer polar form of glioblastoma, in which the cells have a single process. Some of the cells are round or oval, some pear-shaped, some elongated (Fig. 490).



FIG. 490.—Glioblastoma multiforme. The cells vary greatly in shape: some are round, some are elongated, and some are pear-shaped.  $\times 700$ .

They are bipolar spongioblasts when stained by Cajal's gold-sublimate method. There are also tumor giant cells with many nuclei. Mitoses are common. There are no glial fibers, for the spongioblast does not produce such fibers. The vascular endothelium often shows a remarkable proliferation so that the lumen of the vessels may be filled with masses of cells. This change may be observed in still normal tissue beyond the limits of the tumor. One can but guess at the significance of such a change. Around the tumor there is usually well-marked gliosis.

**ASTROCYTOMA.**—The astrocytoma is a comparatively benign tumor. The average time of survival after operation is six years (Cushing), and many of the patients appear to be completely cured. The tumor blends so gently with the surrounding tissue that no line of demarcation can be drawn. It is usually much firmer than the glioblastoma owing to the fibrils

of which it is composed. The tumor may occur in any part of the brain. A common site is the cerebellum, especially in children. A distinction must be drawn between astrocytoma of the cerebrum in adults and astrocytoma of the cerebellum in children. The latter is the purest form of astrocytoma, often shows marked cyst formation, and is the most satisfactory glioma known to the surgeon. Most of the lesion may be represented by a cyst, with only a small nubbin of tumor left in the wall. Small intraneoplastic cysts may be due to degeneration, but larger cysts, which are often outside the tumor, contain fluid which appears to be a transudate from the surface, and which rapidly accumulates after the cyst is aspirated. Astrocytoma of the cerebrum in adults may be much more

cellular, and in places there may be an apparent transition towards glioblastoma.



FIG. 491.—Astrocytoma.  $\times 500$ .

The microscopic picture in a typical case forms a striking contrast to the glioblastoma (Fig. 491). The cells are few, and are uniform in size and shape. Sometimes, however, as the result of degenerative changes, there is swelling and hyalinization of the cell body, and displacement of the nucleus to the side (Fig. 492). As already mentioned, in the cerebrum the tumor may be more cellular, and mitoses may occasionally be seen. The cells are separated by numerous glial fibrils, which are well stained with phosphotungstic acid hematoxylin, but are best shown by the

gold method. (Fig. 493.) Neoplastic astrocytes, being often packed together, may be much more elongated than those of the normal brain. Moreover, they are often lacking in vascular footplates, which are always present in normal astrocytes. Blood vessels are not numerous. A feature characteristic of astrocytoma is the survival of occasional nerve cells in the midst of the tumor; this must be attributed to lack of destructive power on the part of the tumor. Calcification is not uncommon, and may be seen in the roentgen-ray picture. There is no gliosis around the tumor, and it may be very hard to tell the limits of the growth.

**MEDULLOBLASTOMA.**—This highly malignant and rapidly-growing tumor usually occurs in children in the mid-line of the cerebellum (roof of fourth ventricle). It forms a soft reddish-gray mass which may fill the cavity of the fourth ventricle, producing marked hydrocephalus. It is the killing tumor of the child, just as glioblastoma is the killing tumor of the adult. In view of the fact that a tumor in the roof of the fourth ventricle of a child may be the extremely malignant medulloblastoma or the extremely

innocent astrocytoma, biopsy confirmation of the tumor type is of great importance. The latter can be treated with complete success, whereas if the former is interfered with it is likely to be spread throughout the sub-arachnoid space. The medulloblastoma is the only glioma which penetrates the pia and invades the subarachnoid space diffusely. The *microscopic picture* is completely undifferentiated, like that of a round-cell sarcoma. The tumor is extremely cellular and there are no fibrils. The cells are round, but some may be carrot-shaped. The cells may be grouped around blood vessels, forming "pseudorosettes." These differ from the true rosettes of an ependymoma in having no lumen in the center.

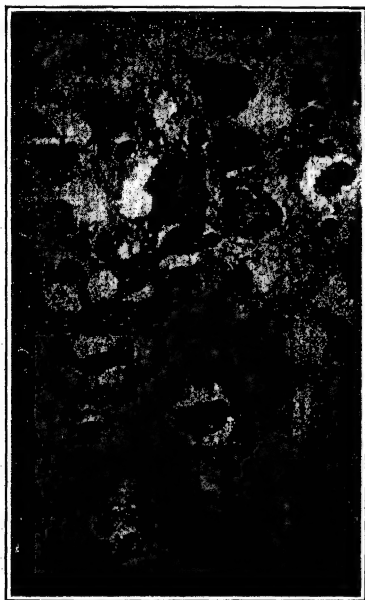


FIG. 492.—Degenerated astrocytes in astrocytoma.  $\times 400$ .



FIG. 493.—Astrocytoma; Cajal's gold-sublimite method.  $\times 300$ .

**EPENDYMOMA.**—This tumor is considerably more rare than the three preceding ones. It resembles the medulloblastoma in usually occurring in children and in the roof or floor of the fourth ventricle, but differs from it in being much less malignant and more highly differentiated. It may grow in the cerebrum close to the lateral or third ventricle. The tumor is fairly firm, and calcification, evident in the roentgen-ray picture, is quite common. *Microscopically* the tumor consists of ependymal cells or more primitive ependymal spongioblasts; the latter are tadpole-shaped, with an elongated tail. As the normal function of ependymal cells is to line a cavity, some of the tumor cells are grouped around small canals; these groups are known as rosettes, and when present in typical form are pathognomonic of ependymoma (Fig. 494). Between the nucleus and the lumen the cytoplasm may contain tiny rods known as blepharoplasten. These

are characteristic of ependymal cells, being the remains of chromatin granules at the base of the cilia.

**ASTROBLASTOMA.**—A rare and relatively benign tumor composed of cells like astroblasts. The cells are attached to vessels by a large vascular process, and as these are not seen in ordinary preparations, the vessels seem to be surrounded by mantles of cells, but separated from them by a clear space.



FIG. 494.—Ependymoma of fourth ventricle in a boy, aged two years. The tumor cells are grouped around a lumen. Blepharoplasten can be seen in the cytoplasm close to the lumen.  $\times 1000$ .



FIG. 495.—Oligodendroglioma.  
 $\times 500$ .



FIG. 496.—Pinealoma.  $\times 400$ .

**OLIGODENDROGLIOMA.**—A very rare tumor of the oligodendroglia, confined to the cerebral hemispheres of adults. Although extremely cellular (Fig. 495), it is slowly growing, and shows a marked tendency to perivascular calcification which can be recognized in the roentgen-ray picture. In ordinary sections the cell bodies are represented by clear spaces like vegetable cells. To prove the nature of the tumor the cell processes must be stained with silver.

**PINEALOMA.**—This is another very rare tumor which grows from the pineal body. It occurs for the most part in the second decade, and is marked by symptoms of involvement of the corpora quadrigemina (oculomotor palsies, deafness), and *pubertas præcox*, *i.e.*, precocious sexual development and adiposity. Hydrocephalus is marked owing to the position of the tumor. The tumor may be regarded as an "adenoma" of the pineal, for it consists of the two types of cells normally present, very large pineal cells and small round neuroglial cells (Fig. 496).

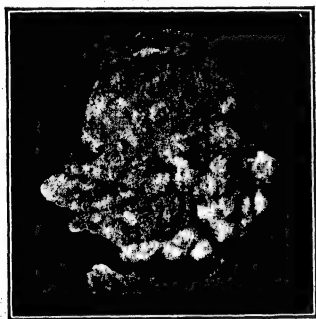


FIG. 497.—Pearly tumor (cholesteatoma.)



FIG. 498.—Retinoblastoma.

**CHOLESTEATOMA.**—This rare tumor is of developmental origin, arising from epithelial implantations which occur in the development of the embryo. The common site is under the pia, but it may be in the substance of the brain or in one of the ventricles. Depending on the time that the cellular anlage is cut off, the capsule may be either purely epidermal or dermal with hair follicles. In the later case the tumor will be a *dermoid cyst* with the usual buttery contents and wisps of hair. In the much commoner epidermal form the lesion is covered by stratified epidermal cells, which become desquamated and cornified. The gross appearance is highly characteristic, and has earned for the lesion the name of *pearly tumor* (Fig. 497). The tumor is globular, and the surface is smooth, silky, of a mother-of-pearl luster, and may present pea-sized elevations. The surface can be picked off in flakes. Microscopically the tumor consists of layers of polygonal cells filled with granules, fatty material, and cholesterol crystals.

**GANGLIONEUROMA.**—This is perhaps the rarest of brain tumors. It is composed of adult nerve cells, and is more likely to be found outside the brain, *e.g.*, in the adrenal medulla (Fig. 145, page 262).

**RETINOBLASTOMA.**—This tumor is commonly called *glioma of the eye*, but it contains no glial fibers, and as it seems to develop from the retinal anlage of the embryo

it seems better to call it a retinoblastoma (Fig. 498). Owing to the presence of "rosettes" of columnar cells, it has been regarded as a *neuroepithelioma*. It is the second commonest tumor of the eye, malignant melanoma being the commonest. It is locally destructive, and in the later stages may metastasize to lymph nodes and internal organs, thus proving that it is not a glioma. The tumor consists of small round cells consisting of little more than nuclei, with hardly any cytoplasm and no fibrils. The rosettes when present are characteristic circular structures composed of columnar cells which probably have a tendency to develop into rods and cones. They are often absent. The tumor nearly always occurs before the fourth year, so that it may be regarded as of congenital origin; it is bilateral in 20 per cent of cases; it displays a remarkable and tragic familial tendency, 10 children out of 16 in one family having died of this tumor.

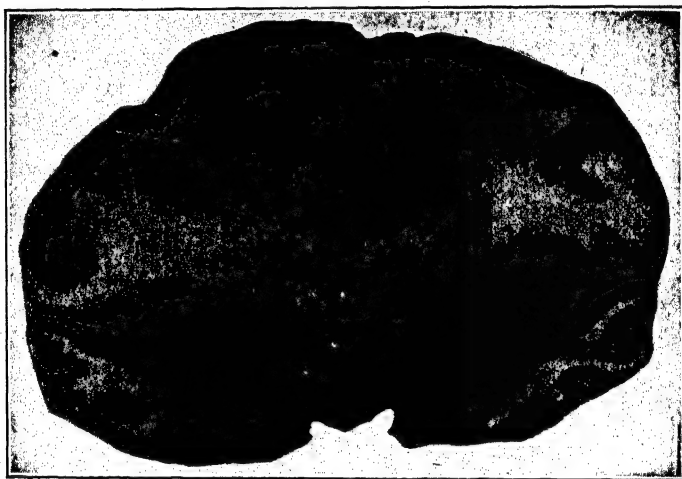


FIG. 499.—Meningioma. The tumor has formed a large depression for itself in the hemisphere, and has caused much distortion of the brain.

**Sheath Tumors.**—It has already been pointed out that it is convenient and logical to divide intracranial tumors (with the exception of pituitary tumors which have already been considered in Chapter 28) into brain tumors proper and tumors of the sheaths of the brain. The latter comprise the meningioma and the acoustic nerve tumor.

**MENINGIOMA.**—This is an innocent tumor (although rarely it may become malignant) and it constitutes one of the commonest forms of intracranial neoplasm. It may be related to trauma. I have seen a meningioma develop at the exact site of a traumatic scar four years after a blow on the head. There is about one meningioma to every four gliomas. The term meningioma is hardly satisfactory from a histogenetic standpoint, but it has the advantage of being non-committal. The tumor arises from groups of mesothelial cells which cover the arachnoid villi and the Pacchionian bodies, and may be regarded as a meningeal fibroblastoma. On account of their mode of origin the tumors are usually situated near the superior longitudinal sinus in the fronto-parietal region; but they may grow from



the falx cerebri, or at the base of the skull in the anterior and middle cranial fossa.

The *gross appearance* is very characteristic, for the tumor presses on the brain from the outside and forms a deep bed for itself, from which in the autopsy room it can be readily shelled out (Fig. 499). In the operating room, however, things are far less simple, and the surgeon may readily lose his patient from hemorrhage from large vessels which pass between the highly vascular overlying bone and the tumor. The meningioma is usually much firmer than the glioma. It is adherent externally to the dura. It remains encapsulated, and does not penetrate the pia nor infiltrate the brain, so that it lends itself to surgical removal. *Microscopically* it

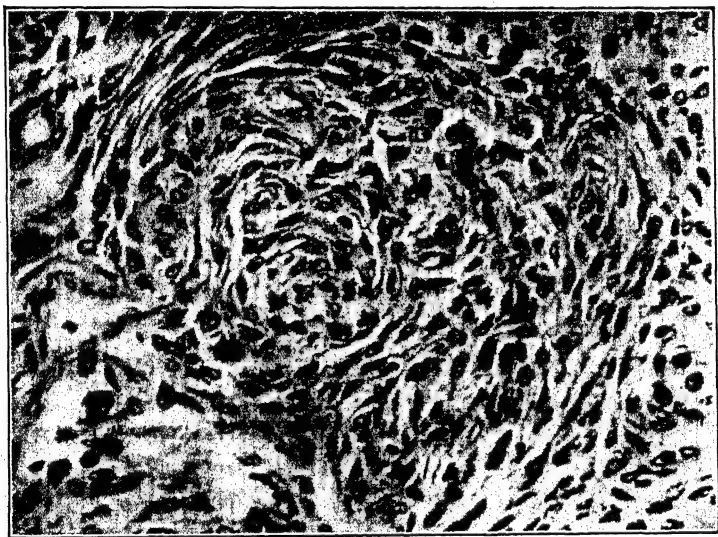


FIG. 500.—Meningioma. The whorled arrangement of the elongated cells is plainly shown.  $\times 400$ .

consists of elongated fibroblastic cells often showing a whorled arrangement (Fig. 500). The whorls may undergo hyaline degeneration and form little masses like epithelial pearls. These may become calcified and resemble corpora amylacea, giving an appearance known as psammoma bodies or brain sand (*psammos*, sand), and on this account the tumor used to be known as a *psammoma*. In rapidly-growing tumors the cells may be rounder and much less differentiated. Occasionally fat may be present (*lipo-meningioma*). *Local changes in the skull* may be of great help in diagnosis. In about 25 per cent of cases there is bony thickening over the tumor which can be detected radiologically and sometimes clinically. This is due to penetration of the dura by the tumor and invasion of the skull, with ossification of the stroma of the invading tumor. In rare cases there may be erosion and perforation of the bone in place of thickening.

ACOUSTIC NERVE TUMOR.—This is the second of the sheath tumors, and it resembles the meningioma in many respects. Occurring in the cerebello-pontine angle and growing from the sheath of the acoustic nerve, it forms a firm, round, well-encapsulated tumor, which presses on the brain stem and produces marked distortion and displacement of that structure (Fig. 501). A similar tumor sometimes grows on the roots of the spinal nerves. There is difference of opinion regarding the origin and nature of these tumors. It is usually regarded as a fibroblastoma arising from the



FIG. 501.—Acoustic nerve tumor. The tumor has produced marked distortion of the brain stem.

perineurium of the nerve, but Masson believes that it is a tumor of the cells of the sheath of Schwann, what the French writers call a Schwannoma. It is identical in structure with the perineurial fibroblastomas (solitary neuromas) growing on peripheral nerves. The subject is discussed further in connection with tumors of nerves. *Microscopically* it consists of elongated nuclei often arranged side by side so as to produce a characteristic banded or "palisade" appearance. There may also be eddies or whorls of cells. The outline of the cells is vague, and the background is fibrous in character, probably collagen. The *clinical effects* are facial palsy and nerve deafness

(seventh and eighth nerves), and the usual signs of intracranial tumor. These effects are the result of involvement of the fifth, seventh and eighth nerves, as shown by numbness along the jaw and side of tongue, some facial weakness, and deafness. In addition there are the usual signs of intracranial tumor. An important feature is a nearly invariable increase of the protein in the cerebrospinal fluid, although in one of our cases it was normal. It can at least be said that a normal fluid in a posterior fossa tumor nearly always means an intracerebellar lesion. The protein increase may be attributed to blockage of the circulation of cerebrospinal fluid to the spinal subarachnoid space or to compression of the venous channels draining the choroid plexus.

**HEMANGIOMA.**—Vascular tumors of the brain can be divided into (1) angiomatous malformations and (2) hemangioblastomas. Each group includes a general systemic disorder as well as the local cerebral lesion. The first condition is a cavernous angiomatosis of the brain; it is associated with a similar condition of the skin and with congenital glaucoma. The second is a capillary angiomatosis of the cerebellum and is associated with similar lesions of the retina and some of the viscera. The kidneys and the pancreas may be cystic. This angiomatosis of cerebellum and retina is known as *Lindau's disease*. In one case which I studied the mother, a brother and a sister suffered from lesions both of the cerebellum and retina. In this case the pancreas was a mass of cysts, and many were present in the renal cortex. It is hereditary in character, occurring in one family in three generations. Sometimes the lesions are in the medulla or cord instead of the cerebellum; they never occur in the cerebrum. The tumor is composed of angiomatous spaces between which are xanthoma-like cells filled with lipid (Fig. 502).



FIG. 502.—Lindau's disease.  $\times 85$ .

**Secondary Tumors.**—When a diagnosis is made of tumor of the brain it must not be forgotten that the tumor may be secondary. The most common site of the primary tumor is the lung. In a series of 82 cases reviewed by Dr. Mary Tom in my department in Toronto the percentage as regards the primary site was as follows: lung, 22; breast, 15; large intestine, 11; malignant melanoma, 8. The secondary tumors are often multiple. The course of the disease is apt to be more acute than in the case of a primary tumor. *Diffuse involvement of the meninges* may be the result of invasion of the subarachnoid space by a glioma (usually a medullo-

blastoma) or a secondary tumor (often a melanoma); sometimes the melanoma seems to originate in the meninges. A mantle of tumor cells may cover the brain and even the cord, and tumor cells may be found in the spinal fluid obtained by lumbar puncture. The methods of exfoliative cytology which have proved of such value in other regions of the body may enable a diagnosis of metastatic tumor to be made even in the absence of widespread meningeal involvement. The best results are obtained with wet stained films (McCormack *et al.*). The sugar values in the cerebrospinal fluid are likely to be low. The method is also of value in primary brain tumors.

### SPINAL CORD TUMORS

Tumors of the spinal cord are rare in comparison with tumors of the brain. The symptoms are of much longer duration, the history sometimes extending over a considerable number of years. The surgical prospect is much better than in the case of the brain, especially in the extramedullary tumors. The cord may be severely compressed, and yet when the tumor is removed function may return to an astonishing degree. The usual sequence of events, especially in extramedullary tumors, is first root pains, then the Brown-Séquard syndrome (paralysis of motion and deep sensation on the side of the tumor, loss of pain and temperature sense on the opposite side), and finally paralysis of the organic and deep reflexes. The *cerebrospinal fluid* may show the "compression syndrome" if the canal is blocked. In the cul-de-sac below the obstruction the characters of the fluid are as follows: (1) massive spontaneous coagulation; (2) xanthochromia or yellow coloration of the fluid; (3) marked increase in the protein; (4) no corresponding increase in the cells. This is known as the Froin syndrome, of which only the last two features may be present. The presence of a block can also be shown by the Queckenstedt sign (absence of the normal rise in spinal pressure when both jugular veins are compressed). The exact site may sometimes be determined by the intraspinal injection of lipiodol followed by radiography. Lumbar puncture is, therefore, of great value in the diagnosis of suspected spinal cord tumors. It should not be done in suspected brain tumors, especially if the tumor is believed to be in the posterior cranial fossa, because of the danger of pressure on the medulla if the brain stem is displaced downward into the foramen magnum. The tumor may be extramedullary or intramedullary; the extramedullary tumors may be extradural or intradural.

**Extramedullary Tumors.**—These tumors are frequently benign in character, and there may be an interval of several years between the root symptoms and the appearance of any sign of pressure on the cord. Even when marked pressure has developed there may be little or no degeneration of the cord. Neurofibromas are the commonest, followed by meningiomas, and then by intramedullary tumors, of which the most frequent are ependymomas. *Extradural tumors* are uncommon. They are often sarcomatous in character, arising either from the outer surface of the dura or from the vertebræ. *Intradural tumors* form the main bulk of spinal cord tumors. The growth is usually benign in character, being either a meningioma or a perineurial fibroma of the nerve roots similar in character to the acoustic

nerve tumor (possibly a Schwannoma). The tumor is usually oval, seldom grows to a large size, and shows absence of the normal cord pulsation. The cord may be seriously compressed, but is seldom invaded by the tumor.

**Intramedullary Tumors.**—These tumors are gliomas. Practically all the forms which have been described as occurring in the brain may be found in the cord. Perhaps the commonest is the ependymoma, which arises from the ependymal cells of the central canal. The tumor extends up and down the cord rather than horizontally, and the overlying dura may appear normal. Absence of pulsation indicates the lesion when the surgeon opens the spinal canal.

## THE NERVES

**INJURY AND REPAIR.**—The effects of injury can be best studied in section of a peripheral nerve. Attention may be confined to one of the individual fibers of which the nerve is composed. When a nerve fiber is divided from its cell of origin the distal part undergoes the changes known as Wallerian degeneration, which have already been described in connection with the general pathology of the nervous system. It will be recalled that all three components of the fiber share in these changes. The axis cylinder disintegrates and disappears, the medullary sheath breaks up into droplets of myelin, and the cells of the sheath of Schwann proliferate and exert a phagocytic action on the degenerated myelin. Similar changes occur in the proximal part up to the first node of Ranvier.

But combined with the degenerative changes there is soon evidence of attempts at *repair*, just as inflammation of any tissue may pass imperceptibly into regeneration. The proliferated Schwann cells in both proximal and distal ends become arranged in the form of a tube along which new axis cylinders may grow out once more to the periphery. For long there was great difference of opinion as to whether the regeneration was *peripheral*, the new fibers being laid down by the Schwann cells (neurilemma) and joining up later with the proximal end, or *central*, the new fibers being formed as outgrowths from the divided proximal end. Modern opinion is entirely in favor of the central view, but it must be admitted that it is sometimes difficult to account for the speedy return of function which may follow division of a nerve on the hypothesis that the new fibers have grown from the site of the lesion to the motor or sensory end-organ concerned.

In the course of a few days the axis cylinder proceeds to grow out as a bulbous process in search of the missing distal end. This search will be unsuccessful if the distance between the two ends is more than an inch, or if the ends are separated by scar tissue. The surgeon may transplant a piece of nerve to close the gap when it is unduly large, but this piece merely acts as a bridge along which the new fibers may travel to the distal part. When the bulbous end of the axis cylinder reaches the distal portion it puts out fine fibrils which grow down the tubular sheath formed by the proliferated Schwann cells. These fibrils reestablish the continuity of the pathway and become clothed again, with the assistance of the Schwann ends, by a medullary sheath. If the distance is too great to be bridged or if the part supplied by the nerve has been amputated, the axis cylinder may coil up so as to form a nodule capped by fibrous tissue. Such a mass at the end of a nerve, composed of nervous and fibrous tissue, is called an *amputation neuroma* (stump neuroma). Some degree of sensation may reappear fairly quickly, but complete restoration of function, even when the cut ends are brought into accurate apposition, seldom occurs in less than three or four months.

The process which has just been described is only seen in the peripheral nerves. In the central nervous system the fibers do not possess a sheath of Schwann, so that while Wallerian degeneration takes place as before, real repair is impossible.

**Neuritis.**—The term neuritis signifies inflammation, but the lesions are for the most part degenerative rather than inflammatory. Direct infection of a nerve produces true inflammation known as *interstitial neuritis*, and likely to be confined to a single nerve. The degenerative form is known as *toxic neuritis*, because it may be caused by diffusely acting toxins. It is therefore frequently multiple, and is known clinically as *multiple peripheral neuritis* or *polyneuritis*.

Polyneuritis can be produced experimentally by means of a diet deficient in Vitamin B<sub>1</sub>. Similar lesions are seen in cases of human avitaminosis, such as beri-beri. It is probable that dietary deficiency is a commoner cause of polyneuritis than was formerly believed. For instance alcoholic neuritis is now thought to be due to avitaminosis caused by chronic gastritis and consequent interference with digestion. Such cases might better be called *polyneuropathy* than *polyneuritis*.



FIG. 503.—Demyelination in toxic neuritis.  $\times$  510.

**TOXIC NEURITIS.**—The toxins which cause this common form of neuritis may be inorganic or organic. A long list of poisons could be given, but the more important ones are lead, arsenic, alcohol (?avitaminosis), diphtheria toxin, and some metabolic poison produced in diabetes. Neuritis may follow septic conditions and many of the infectious fevers. In some cases no cause can be found. It is the small nerve twigs which are affected first and to the greatest degree, so that the term *peripheral neuritis* is well chosen. As the nerve is traced upward the condition becomes progressively less. The changes are similar to those of Wallerian degeneration following division of a nerve, but are less severe and complete. The axis cylinders degenerate and may show varicose swellings, but they do not disappear. The medullary sheath breaks up into droplets of myelin (Fig. 503). The Schwann cells proliferate and become phagocytic for the degenerating myelin.

The muscle fibers supplied by the degenerated nerve show fatty and other retrogressive changes. As the nerve degeneration is seldom complete, recovery is the rule. But if the action of the toxin is long-continued, the interstitial connective tissue may proliferate and may replace the nerve fibers, with permanent impairment of function. The *symptoms* depend on the type of nerve affected. There may be paralysis and wasting of muscles (dropped wrist and dropped foot in alcoholic or lead neuritis), anesthesia, incoördination, loss of reflexes, and trophic disturbances.

**INTERSTITIAL NEURITIS.**—This form of neuritis is usually caused by bacterial invasion of the nerve from some neighboring septic focus, so that

the distribution is asymmetrical, although more than one nerve may be involved. Other forms of irritant are cold, which is a common cause of facial nerve paralysis (Bell's palsy), and pressure from a crutch. The nerve is swollen and red. The interstitial tissue is congested and infiltrated with leucocytes, or may show little beyond edema. The exudate may be confined to the sheath of the nerve. The medullary sheaths of the fibers may undergo some secondary degeneration, but the axis cylinders preserve their integrity, so that when the pressure of the exudate is withdrawn there is restoration of function. The Schwann cells proliferate and take on a phagocytic function.

**ACUTE PORPHYRIA.**—A mysterious and fortunately rare malady which presents clinical features suggestive of polyneuritis is acute porphyria. It generally begins with symptoms suggestive of an ascending paralysis, such as pain and weakness in the extremities. Other features are colicky abdominal pains, mental symptoms, and epileptic seizures. The urine is a port-wine red, but may be colorless, only turning the characteristic color when exposed to sunlight. The condition is really an acute exacerbation of a chronic condition characterized by the passage of a porphyrin in the urine. The nervous system lesions are degeneration of the peripheral and sympathetic nerves, and of cells in the anterior horns and various parts of the brain. Degenerative lesions are also found in the liver, spleen, kidneys and muscles.

**GUILLAIN-BARRÉ SYNDROME.**—This is another condition in which lesions are found both in the nerves and the central nervous system. It is also known as acute infective polyneuritis and is believed to be due to a neurotropic virus. Recovery is usual in a matter of months, but bulbar involvement may cause death. The symptoms are both motor and sensory. There is a slowly ascending flaccid paralysis with loss of deep reflexes, paresthesias and severe root pains. Lesions are found in the nerves, nerve roots, cord, brain and meninges. The nerve and cord lesions are degenerative, whilst in the nerve roots and meninges lymphocytic infiltration is the principal finding.

**Tumors.**—The tumors of nerves form a remarkably confusing and complex subject regarding which a large amount might be said without adding very much to the reader's knowledge. Newer staining methods and increased knowledge of nerve histology should have brought better understanding, but they have served rather to make confusion worse confounded. "The histology of the nerve trunk seems quite simple and well understood if one reads but a single authoritative paper on the subject, but should one read several it will take on more and more complexity" (Foot). The chief cleavage of opinion is as to which constituent of the nerve the neurinoma or ordinary nerve tumor arises from. This is commonly believed to be the connective tissue of the perineurium (Mallory, Penfield), and the tumor is, therefore, called perineurial fibroma or fibroblastoma. On the other hand Masson and other members of the French school maintain that it arises from the cells of the sheath of Schwann, and call it a Schwannoma. This cleavage may be illustrated by the fact that in 1940 Tarlov published a paper proving that by a special silver technique it was possible to differentiate the fibroblasts of the nerve from the Schwann cells, and that only fibroblasts were present in neurinomas which are, therefore, perineurial fibroblastomas, whereas in the very next paper in the same journal Murray

and Stout, employing tissue culture technique to differentiate the two types of cells, proved that the tumors are Schwannomas! Disregarding controversy and employing generally accepted terms the following main types may be recognized: (1) neurofibroma (perineurial fibroma, neurinoma, Schwannoma) a conventional name indicating a nerve tumor resembling a fibroma without regard to its cell of origin; (2) neurofibromatosis (Von Recklinghausen's disease); and (3) neurogenic sarcoma.

No matter which view may be adopted, an examination of the different tumors will show the following common features: long, slender, wire-like

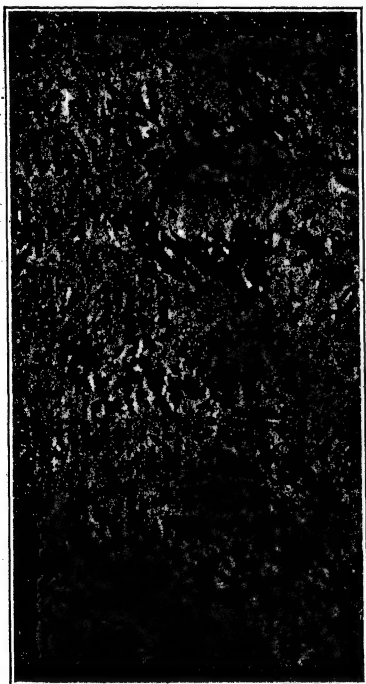


FIG. 504.—Neurofibroma (Schwannoma) showing palisading of nuclei.  $\times 225$ .

fibers with elongated nuclei which have a tendency to be arranged in parallel or palisade fashion (Plate XXX and Fig. 504); in addition to the palisading, which always suggests a nerve sheath origin, the nuclei may be grouped in eddies and streams. The more benign the tumor, the more pronounced are these features. The palisading is perhaps best seen in the acoustic nerve tumor and the similar tumors which occur in the spinal nerve roots, while the whorls are characteristic of meningioma. In the more malignant forms these characters tend to be lost. Penfield and Young have recorded a case of multiple neurofibromata, acoustic nerve tumor, similar tumors on several of the other cranial nerves, and multiple meningiomas.

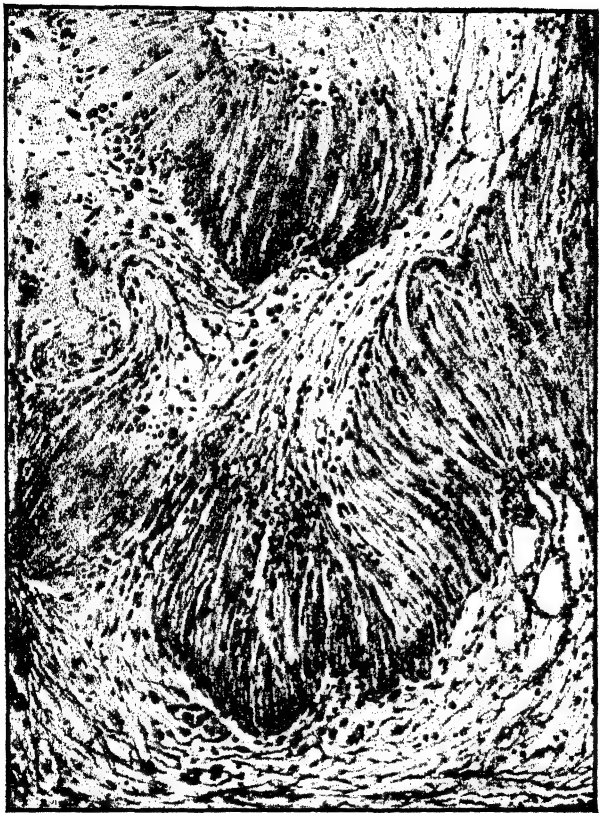
**NEUROFIBROMA.**—This is a benign tumor which forms a round or fusiform firm white mass on the course of one of the larger nerves. It is attached to the sheath of the nerve, but the nerve fibers are not incorporated in the tumor, so that the

term perineurial fibroma appears to be justified. *Microscopically* it is composed of long slender cells, the elongated nuclei of which are arranged in palisades or show whorls and eddies. This structure is identical with that of the acoustic nerve tumor, which also is a perineurial fibroma.

**NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE).**—In this peculiar and often familial condition there are large numbers of tumors, sometimes several hundreds of them, growing from the fine cutaneous nerves, so that the condition is also known as multiple neurofibromata. They form soft nodules in the skin (*molluscum fibrosum*), and may be distributed over the entire body. The skin is often pigmented in patches, or there may be groups of brown spots like freckles. Moreover some mem-



## PLATE XXX



Neurofibroma

Marked palisade arrangement of the cells. (Masson's trichrome green.)

bers of a family may develop nerve tumors, while others only have spots of pigment. Peculiar soft overgrowths of connective tissue may occur, causing great enlargement of a limb, a form of elephantiasis. It is probable that the terrible deformities of the Elephant Man in Treves' story were due to this cause. Megacolon, giant appendix, and other similar overgrowths have been described in connection with similar lesions of the visceral nerves. It seems justifiable to regard the condition as more of a connective-tissue reaction that is part of a general process than as a simple tumor, neurofibromatosis rather than neurofibroma. Acoustic nerve tumor and meningioma may be associated with the condition, and there is always some intermingling of perineurial fibromatous tissue. *Microscopically* the same general picture is seen once again, but the structure is much more mixed. The characteristic tissue has a tangled or reticular structure, which suggests a malformation rather than a neoplasm; this tissue does not show palisading or whorls. It often undergoes a jelly-like hyaline degeneration. Superimposed on this reticular tissue is a varying amount of tissue of neurofibromatous type with palisades and whorls. When special stains are used nerve fibrils can be seen passing through the mass; this never occurs in a neurofibroma. It would appear that in Von Recklinghausen's disease all the elements composing the nerve are involved in some degree, possibly due to failure of the insulating function of the sheath of Schwann.

Although multiple neurofibromas occur especially on the cutaneous nerves, they are also found on the deeper and visceral nerves as well as on the cranial nerves. These deeper growths are prone to undergo sarcomatous change, and this is a frequent cause of death in Von Recklinghausen's disease. Sometimes there is a diffuse neurofibromatosis with widespread overgrowth of the endoneurium and separation of the nerve fibers, a condition known as *plexiform neuroma*. This usually occurs in the head and neck, especially in the distribution of the fifth cranial and upper cervical nerves. Sometimes the main nerve trunks are involved, a condition which is often familial and to which the misleading name of *familial hypertrophic neuritis* has been given in the past.

**NEUROGENIC SARCOMA.**—Malignant tumors may arise from neurofibromas and from neurofibromatosis. Ewing and other members of the Memorial Hospital group also believe that the great majority of what have formerly been regarded as fibrosarcomas of the soft parts are derived from nerve sheaths and should be called neurogenic sarcomas, although no connection with nerves may be demonstrable. They form single, slowly-growing, infiltrating tumors, usually in the subcutaneous and intermuscular tissue of the arm and leg, the commonest location being the thigh. More rarely they occur in the viscera. *Microscopically* the tumor consists of elongated cells or fibers arranged in interlacing bundles and whorls showing a "curly" arrangement, in contrast to the parallel disposition of the fibers of a fibroma, and appearance always suggestive of a neurogenic origin (Fig. 505.) There is not the palisading of a neurofibroma, the cells are more swollen, and there may be mitotic figures.

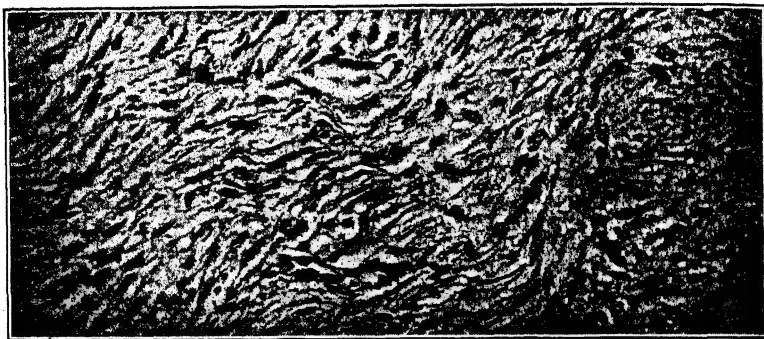


FIG. 505.—Neurogenic sarcoma showing the fasciculated arrangement.  $\times 300$ .

## DEFECTS OF DEVELOPMENT OF THE NERVOUS SYSTEM

**BRAIN.**—*Anencephaly* is a condition in which the cranial vault is deficient and practically the entire brain is missing with the exception of some nervous tissue at the base of the posterior cranial fossa. The spinal cord may be absent except for some flattened plates of nerve tissue, yet the nerves are well developed, as is the body in general. The explanation of this is not evident. There is a remarkable atrophy of the adrenal cortex in the anencephalic monster; the nature of this atrophy is discussed in Chapter 28. The condition is incompatible with life. There may be a deficiency in the skull, usually in the line of a suture, with protrusion of the contents of the cranial cavity. A protrusion of the meninges is called a *meningocele*, which is a sac filled with cerebrospinal fluid and communicating with the subarachnoid space. An *encephalocele* is a protrusion of the brain substance, a condition often associated with and dependent upon hydrocephalus. *Microcephaly* is a condition in which the brain, usually the cerebral hemispheres, remains small. The convolutions may not develop, a condition of *microgyria*. *Porencephaly* is a lack of development of a superficial part of a hemisphere; the resulting space is filled with fluid, covered by membranes, and usually communicates with the lateral ventricle.

*Amaurotic family idiocy* may be mentioned here, as it is essentially a congenital defect. It is also known as Tay-Sach's disease, is congenital in character, and confined to Hebrew infants. The first-born are rarely affected, but when one child has had the disease the subsequent children seldom escape. The symptoms are idiocy, muscular weakness, and rapidly developing blindness (amaurosis), so that the disease is well named. There is a characteristic cherry-red spot at the macula. The brain is small and hard. There is widespread degeneration of the cells and fibers of the cerebral cortex, the anterior and posterior horns of the cord, and the posterior root ganglia. The affected cells both in the brain and in the retina are filled with lipid (Fig. 506). *Tuberous sclerosis* is a congenital condition in which tumor-like masses of neuroglia are scattered through the brain. The glial cells are chiefly large astrocytes. The condition is often associated with congenital malformations and tumors in other organs, more particularly with rhabdomyoma of the heart. *Hydrocephalus* is commoner than any of the above conditions, but it has already been described earlier in this chapter.

**SPINAL CORD.**—The spinal canal may remain entirely open especially in the lumbar region, a condition known as *rhachischisis* and often associated with anencephaly. *Spina bifida* is a much more common and important condition, in which the neural arches remain open, but the canal is closed by the soft parts. The contents of the canal are protruded under the skin to form a soft mass which at once

calls attention to the condition. Sometimes there is no protrusion and swelling to indicate the defect, so that the lesion is hidden, a condition known as *spina bifida occulta*. Its presence is indicated by a patch of hair on the wrinkled skin covering the defect; this hair may resemble a small tail. As the lower part of the canal is the last to close, spina bifida is commonest in the lumbo-sacral region. As a rule five or six vertebrae are involved, sometimes only one. The condition occurs about once in every 1000 births. The contents of the sac may be of three varieties: (1) meningocele, (2) meningocele, (3) syringomyelocele. In the *meningocele* (myelocele), which is the common form, the cord and the nerves of the cauda equina are spread out on the wall of the sac to which they are attached, producing a dimple of the skin known as the umbilicus. In the *meningocele*, which usually occurs in the sacral region, the sac is formed by a hernial protrusion of the arachnoid, the cord or cauda equina remaining within the vertebral canal. The *syringomyelocele* is a rare form in which there is great distention of the central canal and thinning of the cord tissue, so that the wall of the sac is the wall of the canal and is lined by ependymal cells. Spina bifida is often associated with congenital hydrocephalus. *Sacro-coccygeal tumors* of developmental origin occur at the lower end of the spinal canal. Some of these are true teratomata, containing well-formed adult tissue. Dermoid tumors, lipomas and cysts may be present either inside or outside the canal. Other tumors appear to arise from remains of the neuroenteric canal. Or these remains may be represented by a depression over the tip of the coccyx (the "postanal dimple"), or by a channel lined by skin furnished with hair, sweat and sebaceous glands, and known as the *pilonidal sinus*, pilonidal meaning a nest of hair. The chief symptoms are paralysis of the bladder and rectum, weakness in the muscles of the legs leading to clubfoot, trophic ulcers, etc.; these are caused by pressure on the nerve centers. In spina bifida occulta the symptoms appear to be due to a fibrous cord stretching from the skin through the vertebral defect to be attached to the termination of the cord. As the vertebral column grows faster than the cord, it is evident that there will be an increasing degree of traction on the cord with the production of symptoms which may be very puzzling until the defect is discovered.

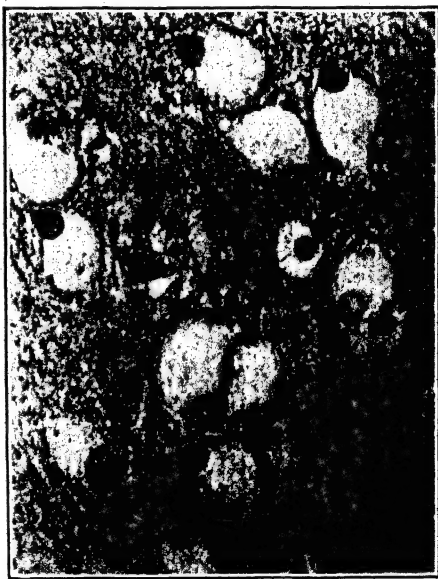


FIG. 506.—Amaurotic family idiocy. The cortical nerve cells are greatly distended with lipid, which displaces the nucleus to one side.  $\times 375$ .

#### ADDITIONAL READING

- Acute Disseminated Encephalomyelitis.** McALPINE: *Lancet*, 1931, 1, 846.  
**Alzheimer's Disease.** MARGOLIS: *Am. J. Path.*, 1953, 29, 588.  
**Arterial Lesions in Tuberculous Meningitis.** DONIACH: *J. Path. and Bact.*, 1949, 61, 253. WINTER: *Am. Rev. Tuberc.*, 1950, 61, 171.

- Astrocytoma.** ALPERS AND ROWE: *Am. J. Cancer*, 1937, **30**, 1.
- Astrocytoma of Cerebellum.** BUCY AND GUSTAFSON: *Am. J. Cancer*, 1939, **35**, 327.
- Avitaminosis in Nervous Disease.** BICKNELL: *Lancet*, 1940, **1**, 10. GREENFIELD: *J. Neurol. and Psychiat.*, 1938, **1**, 306.
- Benign Lymphocytic Choriomeningitis.** ARMSTRONG AND WOOLEY: *J. A. M. A.*, 1937, **109**, 410.
- Cerebral Arteriosclerosis.** SCHEINKER: *Am. J. Path.*, 1946, **22**, 565.
- Cerebral Embolism.** CONE AND BARRERA: *Arch. Neurol. and Psychiat.*, 1931, **25**, 523.
- Cerebral Hemorrhage.** GLOBUS AND STRAUSS: *Arch. Neurol. and Psychiat.*, 1927, **18**, 215.
- Cerebral Softening.** FISHER: *Arch. Neurol. and Psychiat.*, 1951, **65**, 346. HICKS AND WARREN: *Arch. Path.*, 1951, **52**, 408. WEINBERGER, *et al.*: *Arch. Neurol. and Psychiat.*, 1940, **43**, 615, 961.
- Cerebral Toxoplasmosis.** SABIN AND FELDMAN: *Jour. Pediat.*, 1949, **35**, 296. WOLFE, *et al.*: *Am. J. Path.*, 1939, **15**, 657.
- Cholesteatoma.** CUSHING: *Surg., Gynec. and Obst.*, 1922, **34**, 557. LOVE AND KERNOHAN: *J. A. M. A.*, 1936, **107**, 1876.
- Congenital Aneurisms.** Berry Aneurisms. CARMICHAEL: *J. Path. and Bact.*, 1950, **62**, 1.
- Congenital Aneurisms.** BREMER: *Arch. Path.*, 1943, **35**, 819. FORBUS: *Bull. Johns Hopkins Hosp.*, 1930, **47**, 239. GLYNN: *J. Path. and Bact.*, 1940, **51**, 213. TUTHILL: *Arch. Path.*, 1933, **16**, 630.
- Corpora Amylacea.** FERRARO AND DAMON: *Arch. Path.*, 1931, **12**, 229.
- Coxsackie Virus.** DALLDORF, *et al.*: *J. Exp. Med.*, 1949, **89**, 567. GODMAN, *et al.*: *Am. J. Path.*, 1952, **28**, 223.
- Disseminated Sclerosis.** BRAIN: *Quart. J. Med.*, 1930, **23**, 343. SYMONDS: *Brain*, 1924, **47**, 36.
- Drug Encephalitis.** CAVANAGH: *J. Clin. Path.*, 1953, **6**, 128.
- Epidemic Encephalitis.** BOYD: *Quart. J. Med.*, 1924, **18**, 153. HALL: *Epidemic Encephalitis*, Bristol, 1924. ZINSSER: *Arch. Path.*, 1928, **6**, 271.
- Epilepsy.** EARLE, BALDWIN AND PENFIELD: *Arch. Neurol. and Psychiat.*, 1953, **69**, 27.
- Equine Encephalomyelitis.** HURST: *J. Exper. Med.*, 1934, **59**, 529; *J. Path. and Bact.*, 1936, **42**, 271. KING: *J. Exper. Med.*, 1938, **68**, 677.
- Extradural Hemorrhage.** MCKENZIE: *Brit. J. Surg.*, 1938, **26**, 346.
- General Paresis.** STERN: *Brain*, 1932, **55**, 145.
- General References.** BIGGART: *Pathology of the Nervous System*, Edinburgh, 1936. HASEN: *Histopathology of the Peripheral and Central Nervous System*, 2nd ed., Baltimore, 1940. WEIL: *A Text-book of Neuropathology*, Philadelphia, 1933.
- Glioma.** BAILEY: *Intracranial Tumors*, Springfield, 1933. BAILEY AND CUSHING: *A Classification of Tumors of the Glioma Group on a Histogenetic Basis*, Philadelphia, 1926. CARMICHAEL: *J. Path. and Bact.*, 1928, **31**, 493. EISENHARDT: AND CUSHING *Am. J. Path.*, 1930, **6**, 541. ELVIDGE, *et al.*: *Am. Research Nerv. and Ment. Dis.*, *Proc.*, 1937, **16**, 107. KERNOHAN, *et al.*: *Proc. Staff Meet.*, *Mayo Clin.*, 1947, **24**, 54; *Proc. Staff Meet.*, *Mayo Clin.*, 1949, **24**, 71. SCHERER: *Brain*, 1940, **63**, 1. ZIMMERMAN AND MAIER: *Am. J. Path.*, 1949, **25**, 801.
- Hemangioma.** BAILEY AND FORD: *Am. J. Path.*, 1942, **18**, 1. CUSHING AND BAILEY: *Tumors Arising from the Blood Vessels of the Brain*, Springfield, 1928. DAVIDOFF: *Am. J. Path.*, 1929, **5**, 141. LINDAU: *Proc. Roy. Soc. Med.*, 1931, **24**, 363.
- Hemorrhagic Encephalitis.** BAKER: *Am. J. Path.*, 1935, **11**, 185.
- Hepato-lenticular Degeneration.** BAKER: *Arch. Path.*, 1948, **46**, 268. DENNY-BROWN AND PORTER: *New England J. Med.*, 1951, **245**, 917. WILSON: *Brain*, 1912, **34**, 295.
- Herpes Zoster.** CHEATHAM: *Am. J. Path.*, 1953, **29**, 401.
- Huntington's Chorea.** DUNLAP: *Arch. Neurol. and Psychiat.*, 1927, **18**, 867.
- Hydrocephalus.** DANDY: *Ann. Surg.*, 1919, **70**, 129; *Bull. Johns Hopkins Hosp.*, 1921, **32**, 5; *Surg., Gynec. and Obst.*, 1920, **31**, 340. RUSSELL: *Med. Res. Council, Spec. Rep. Series*, No. 265, 1949. WAKELEY AND ALLEN: *Brit. J. Surg.*, 1929, **17**, 278.
- Hypertensive Encephalopathy.** ROSENBERG: *Arch. Int. Med.*, 1940, **65**, 545.
- Internal Carotid Artery Occlusion.** FISHER: *Arch. Neurol. and Psychiat.*, 1951, **65**, 346. HULTQUIST: Über Thrombose und Embolie der Arteria carotis und hierbei vorkommende Gehirnstörungen, Jena, 1942. MONIZ, *et al.*: *Pressé méd.*, 1937, **45**, 977.

- Interrelationship of Diseases of the Liver and the Brain.** BAKER: Arch. Path., 1948, 46, 268.
- Intracranial Aneurisms.** RICHARDSON AND HYLAND: Medicine, 1941, 20, 1.
- Meningioma.** BAILEY AND BUCY: Am. J. Cancer, 1931, 15, 15. CUSHING AND EISENHARDT: Meningiomas: Their Classification, Regional Behavior, Life History, and Surgical End Results, Springfield, Ill., 1938. LAPRESLE, *et al.*: Am. J. Path., 1952, 28, 757.
- Meningitis Following Head Injuries.** LINELL AND ROBINSON: J. Neurol. and Psychiat., 1941, 4, 23.
- Muscular Dystrophies.** BRAMWELL: Lancet, 1925, 2, 1103.
- Nerve Tumors.** FOOT: Am. J. Clin. Path., 1936, 6, 1. PENFIELD AND YOUNG: Arch. Neurol. and Psychiat., 1930, 23, 320.
- Neurofibroma.** BAILEY AND HERMANN: Am. J. Path., 1938, 14, 1. MURRAY AND STOUT: Am. J. Path., 1940, 16, 41. TARLOV: Am. J. Path., 1940, 16, 33.
- Neurogenic Sarcoma.** STEWART AND COPELAND: Am. J. Cancer, 1931, 15, 1235.
- Oligodendroglioma.** BAILEY AND BUCY: J. Path. and Bact., 1929, 32, 735.
- Pacchionian System.** WINKELMAN AND FAY: Arch. Neurol. and Psychiat., 1930, 23, 44.
- Paralysis Agitans.** PARKINSON: Arch. Neurol. and Psychiat., 1922, 7, 681 (photostat copy).
- Pinealoma.** GLOBUS: Arch. Path., 1941, 31, 533. RUSSELL AND SACHS: Arch. Path., 1943, 35, 869.
- Poliomyelitis.** ARMSTRONG: Pub. Health Rep., 1939, 54, 1719 and 2302. CAREY, *et al.*: J. Neuropath., 1944, 3, 121. DOLGOPOL AND CRAGAN: Arch. Path., 1948, 46, 202. DENDST AND NEUBUERGER: Am. J. Path., 1950, 26, 863. FABER AND SILVERBERG: J. Exp. Med., 1946, 83, 329. HURST: J. Path. and Bact., 1929, 32, 457; 1931, 34, 331. LÖBLICH: Virchows Archiv., 1950, 318, 211. RHODES, *et al.*: Canad. J. Pub. Health, 1950, 41, 146. SABIN: J. A. M. A., 1942, 120, 506. TRASK AND PAUL: J. Exp. Med., 1943, 77, 545.
- Porphyria.** BAKER AND WATSON: J. Neuropath. and Exp. Neurol., 1945, 4, 68. DENNY-BROWN AND SCIAERHA: Brain, 1945, 68, 1.
- Postencephalitic Parkinsonism.** HOHMAN: Bull. Johns Hopkins Hosp., 1925, 36, 403. McALPINE: Brain, 1923, 46, 255.
- Postvaccinal Encephalitis.** FLEXNER: J. A. M. A., 1930, 94, 305. PERDRAU: J. Path. and Bact., 1928, 31, 17.
- Rabies.** GOODPASTURE: Am. J. Path., 1925, 1, 547.
- Relation of Trauma to Tumor.** PARKER AND KERNOHAN: J. A. M. A., 1931, 97, 535.
- Schilder's Disease.** SCHATTENBRAND: Arch. Neurol. and Psychiat., 1927, 18, 944. SYMONDS: Brain, 1928, 51, 24.
- Schwannoma.** MASSON: Am. J. Path., 1932, 8, 367, 389.
- Secondary Tumors of Brain.** GLOBUS AND MELTZER: Arch. Neurol. and Psychiat., 1942, 48, 163. McCORMACK *et al.*: Am. J. Clin. Path., 1953, 23, 470. TOM: Canad. Med. Assn. J., 1946, 54, 265.
- Spinal Cord Tumors.** KERNOHAN: Arch. Path., 1941, 32, 843. KERNOHAN, *et al.*: Arch. Neurol. and Psychiat., 1931, 25, 679. RASMUSSEN, *et al.*: Ann. Surg., 1940, 111, 513.
- Spontaneous Subarachnoid Hemorrhage.** STRAUSS, *e. al.*: Arch. Neurol. and Psychiat., 1932, 27, 1080. SYMONDS: Quart. J. Med., 1924, 18, 93.
- Subdural Hemorrhage.** GARDNER: Arch. Neurol. and Psychiat., 1932, 27, 847. LEARY: J. A. M. A., 1934, 103, 897. LINELL: Lancet, 1940, 2, 514.
- Tabes.** STERN: Brain, 1929, 52, 295.
- Theiler's Disease.** SABIN AND OLITSKY: J. Exper. Med., 1938, 67, 201.
- Tuberculous Meningitis.** BERES AND MELTZER: Am. J. Path., 1938, 14, 59. RICH AND McCORDOCK: Bull. Johns Hopkins Hosp., 1929, 44, 273; 1933, 52, 5. SMITH AND VOLLUM: Lancet, 1950, 2, 275. TERPLAN: Am. J. Path., 1953, 29, 616.
- Tuberous Sclerosis.** PRATT-THOMAS: Am. J. Path., 1947, 23, 189.
- Tumors of Peripheral Nerves.** ADAIR AND McLEAN: Am. Research Nerv. and Ment. Dis., Proc., 1937, 16, 440. FOOT: Arch. Path., 1940, 30, 772.
- Wernicke's Disease.** ALEXANDER: Am. J. Path., 1940, 16, 61. WARDENER AND LENNOX: Lancet., 1947, 1, 11.

## Chapter

## 32

### THE BONES

**DESCRIPTIVE OUTLINE.**—In describing disease in bone the following structures should be considered: periosteum, shaft, medullary cavity, epiphyseal cartilages (if still present), epiphyses, and articular cartilage. The bone-marrow varies in different bones and at different ages. In childhood all the marrow is red, but with the approach of adult life the red becomes converted into yellow marrow in the shaft of the long bones. The marrow of the flat bones (skull, sternum, ribs, vertebræ and pelvis) remains red.

### THE PHYSIOLOGY OF BONE

The anatomy of bone is a commonplace subject with which everyone is acquainted. The physiology of bone is a little less familiar. Bone does not serve merely as a rigid support. It is the great calcium and phosphorus reserve of the body, a reserve which is being continually drawn upon or added to, so that its structure is not fixed and permanent. It is composed of living cells and hyaline matrix impregnated with calcium salts. The vital character of bone is illustrated by the words of Sir Charles Bell, written more than a hundred years ago: "Scrape a bone and its vessels bleed; cut or bore a bone and its granulations sprout up; break a bone and it will heal; burn it and it dies." The cells are of two kinds: (1) adult bone cells lodged in lacunar spaces surrounded by matrix; (2) osteoblasts, *i. e.*, osteogenic cells of a specific nature but not completely differentiated, which form a more or less continuous investment for the bone in the deep layer of the periosteum, in the Haversian canals, and in the endosteum. Most of the tissues contain about 6 mg. of calcium per 100 cc., but in bone the figure rises to 10,000 mg. The normal blood calcium varies from 9 to 11 mg., with an average of 10 mg. Under normal conditions a state of equilibrium exists between the calcium in the blood and that in the bones, but in disease it may be seriously disturbed. The calcium is absorbed from the food in the small intestine, and is excreted by the large intestine and to a lesser extent by the kidney. The calcium in the bone is combined with phosphorus in the form of calcium phosphate, which constitutes 80 per cent of the mineral content of the matrix, the remainder consisting of calcium carbonate and magnesium phosphate.

The normal growth of bone is influenced by three vitamins, A, C and D. In Vitamin-A deficiency there is interference with the distribution and intensity of osteoblastic and osteoclastic activity, so that bone development is retarded. In Vitamin-C deficiency (scurvy) there is a failure of synthesis of intercellular collagenous material. In Vitamin-D deficiency (rickets

and osteomalacia) there is interference with the deposition of minerals in the bone.

The complex problem of *ossification* will not be discussed here. It may be said, however, that it is becoming increasingly evident that the deposition of calcium and phosphorus in the osteoid tissue which is the precursor of true bone is a physico-chemical process in which the physico-chemical nature of the matrix is a factor of great importance. This is shown by the experiment of Wells, who transplanted boiled cartilage from one animal into the tissues of another animal, and found that the transplanted material, though dead, soon became calcified. A second factor which determines the laying down of calcium salts is the action of *phosphatase*, an enzyme which hydrolyzes the phosphoric esters into inorganic phosphates. This enzyme is produced by the bone cells, but is most abundant in young growing bones and in the layer immediately below the periosteum which is rich in osteoblasts. It is not present in young cartilage until a center of ossification appears. The much-debated question as to the part which the periosteum plays in bone formation will be discussed in connection with the repair of a fracture. Sometimes *metaplastic ossification* (to be distinguished from metastatic calcification) may occur, owing to a tissue other than osteoid becoming transformed into bone. In this way there may be bone formation in the walls of arteries, in the scars of abdominal wounds, and in the tonsil. It is hard to find a satisfactory explanation of this process.

*Calcification* is the term applied to the deposition of calcium in tissue which is not osteoid. The process is discussed at length in Chapter 2. *Metastatic calcification* occurs when calcium is removed from the bones as the result of some rarefying process and is deposited in other tissues. Hyperparathyroidism affords one of the best examples.

**Absorption of Bone.**—There is no tissue in the body which is capable of so much overgrowth or on the other hand so much absorption as bone. The cause of the absorption may be general (hyperparathyroidism) or local (pressure, etc.). It occurs in old age, from disuse, as the result of acute and chronic inflammation, and due to tumor and aneurism. The removal of the excess callus of a fracture and of a sequestrum (dead bone) are excellent examples. Bone undergoing absorption is softer, more easily cut, and bleeds more readily because of its greater vascularity. It can be recognized in the roentgen-ray picture by the decreased density of the shadow.

There are two chief factors in the absorption of bone: (1) vascular absorption, and (2) the action of osteoclasts. (1) *Vascular absorption* is the powerful factor. In ordinary compact bone the blood vessels run longitudinally in a series of channels called the Haversian canals, around which the bony lamellae are grouped, and transversely from the periosteum in Volkmann's canals. Persistent vascular dilatation is followed by widening of the canals at the expense of the bone, and if inflammatory granulation tissue is formed within them, as in tuberculosis, the absorption becomes very marked, a condition of *rarefaction* or *osteoporosis*. Primary removal of the calcium salts, as in hyperparathyroidism, is also followed by widening of the canals and the formation of granulation tissue within them, but these changes have now become effects rather than causes of the absorption of



bone. This primary removal of calcium is known as *halisteresis* (*hals*, salt; *steresis*, privation) or osteolysis. It would appear that in primary vascular resorption the mechanism by which the calcium is removed and the canals widened is a physico-chemical one. In inflammation there are probably local changes in the hydrogen-ion concentration that lead to solution of calcium and the production of narrow zones of decalcification around the vessels which allow the vascular canals to become dilated. Any local excessive production of carbon dioxide tends to cause solution of calcium, for the solubility is affected directly by the carbon dioxide tension of the blood and tissue fluids. The reaction which takes place at the line of



FIG. 507.—Three multinucleated osteoclasts above and to the left of a bone trabecula, the lower margin of which is lined by osteoblasts.  $\times 300$ .

contact of dead and living bone is of this nature, although inflammation is also a factor here. For these reasons only well-vascularized living bone can be absorbed quickly. Dead bone is absorbed slowly by osteoclasts.

(2) *Osteoclasts* may be absent or they may dominate the process. The osteoclast or bone phagocyte is a large cell with strongly acidophilic and granular cytoplasm; it is often multinucleated, containing a few or a large number of nuclei (Fig. 507). It is from the osteoclasts that the foreign body giant cells of bone are derived. It may show a fringed or toothed border (brush border) along the edge in contact with bone. Howship's lacunæ on the surface under the periosteum are produced by the osteoclasts. The phagocytic action of osteoclasts is most readily studied in the removal of small fragments of bone which have become separated. Large foreign

body giant cells are formed for this purpose. It is probable that decalcification must first occur before the osteoclast can exert its phagocytic action. This chemical change is brought about by the tissue juices, possibly by the osteoclasts themselves.

The calcium balance of the biochemist is paralleled by the osteoclastic resorption and the osteoblastic apposition of new bone, first as a thin seam of osteoid tissue, which goes on throughout life.

The state of calcification of the skeleton is governed largely by the endocrine glands. Of these the most important, of course, are the parathyroids, but the thyroid and adrenal also play a part, as is shown by the osteoporosis of hyperthyroidism and of Cushing's syndrome. Estrogens also influence bone formation. In women postmenopausal osteoporosis is common, and this is alleviated by estrogen therapy, which promotes retention of calcium and phosphorus (Albright). Bone formation seems to be influenced by certain of the steroid hormones, which stimulate the osteoblasts and promote protein anabolism, whereas the "sugar-active" corticoids of the adrenal, which inhibit protein anabolism, depress the activity of the osteoblasts.

Bone consists of an organic protein matrix laid down by osteoblasts, and an inorganic calcium complex (calcium-phosphate-carbonate) deposited in the matrix from the serum. Theoretically, therefore, osteoporosis might be due to: (1) excessive bone resorption, (2) insufficient deposition of the calcium complex, and (3) inadequate formation of the protein matrix.

In actual practice generalized bone deficiency of metabolic origin may take three forms. (1) Generalized osteitis fibrosa, where there is excessive bone resorption associated with compensatory new bone formation. The condition may be due to (a) hyperparathyroidism or (b) renal glomerular failure with phosphate retention. (2) Osteomalacia, where the calcium complex is not deposited in the protein matrix owing to calcium deficiency. There is abundant formation of pale-staining osteoid tissue with corresponding osteoblastic activity. The condition may be due to (a) deficient calcium absorption from the intestine, or (b) various renal tubular deficiencies resulting in excessive loss of calcium in the urine. (3) Osteoporosis, where there is poor formation of the protein matrix of bone, but normal calcium deposition and bone resorption. Osteoporosis may occur in a variety of clinical conditions, of which three deserve special mention. (a) Atrophy of disuse, seen in paralysis or immobilization of a limb. Osteoblasts lack the normal stimulus of stresses and strains, so that bone formation is diminished. (b) Hypercorticism. Osteoporosis is a feature of Cushing's syndrome, which is due to hypersecretion of adreno-cortical hormone with gluconeogenic activity, a hormone which appears to inhibit the activity of osteoblasts. (c) Gonadal deficiency. As osteogenesis is under the control of gonadal hormones, it is natural that osteoporosis should develop as a result of the loss of either estrogens or androgens. The former is much commoner owing to the occurrence of the female menopause. Indeed "post-menopausal osteoporosis" is the commonest metabolic bone disorder (Albright and Reifenstein). Senile osteoporosis is for the most part gonadal in origin. It should be noted that osteoporosis also occurs in men with eunuchoidism and in young women with ovarian agenesis.

**Repair of Bone.**—The repair of bone is best studied in the healing of a fracture, either in human material or in experimental fractures in animals. Adult bone cells have lost the power of proliferation so that they play no part in the regeneration of bone. Repair is carried out entirely by the osteoblasts which line the deep layer of the periosteum, the endosteum, and the Haversian canals. The deep cellular layer of the periosteum is a striking structure which must be seen to be appreciated. It is much more abundant in young bone, and can be seen to react exuberantly after a fracture. Osteoblasts are present both in the periosteum and the surface layer of bone, so that repair can occur either with or without the periosteum. The essential function of the periosteum is to supply the outer part of the bone with blood. Removal or separation of the periosteum is apt to be followed by death of this part of the bone.

**Healing of a Fracture.**—This takes place in three stages: First *granulation tissue* forms in the exudate between the broken ends of bone then *osteoid tissue* is formed, and finally *calcium salts* are deposited with the production of bone. (1) As a result of the fracture, blood and a varying amount of exudate are poured out between and around the ends of bone. This is invaded by cells and new capillaries, and a kind of granulation tissue is produced. The proliferating cells are osteoblasts, derived for the most part from the deep layer of the periosteum. The proliferation of osteoblasts is of an extraordinarily rapid and massive character; indeed, there is no other non-malignant process which is quite comparable with it (Fig. 508, A). (2) In the course of four or five days the osteoblasts form trabeculae around central spaces which become Haversian canals. This is osteoid tissue, *i. e.*, tissue resembling bone in its structural arrangement but with no calcium salts in its homogeneous matrix (Fig. 508, B). The osteoid tissue, also known as *callus*, becomes increased in amount so as to act as a splint. By the end of the second week it is remarkably abundant (Fig. 508, C). (3) Finally calcium is laid down, and the ends are knit together by rigid, fully formed bone (Fig. 508, D). Low blood calcium produced by deficient diet does not slow the rate of healing or lead to non-union. In the immediate neighborhood of the fracture the bone cells die. Near the fracture the osteogenic cells proliferate in massive fashion, and may form cartilage instead of bone. This cartilage formation is most marked when there is movement or separation of the fragments. The new cartilage is invaded and replaced by bone. This is ossification in cartilage, as compared with the process just described which corresponds to ossification in membrane.

Changes in the hydrogen ion concentration influence the process. The pH is first acid, favoring decalcification. At the end of a week it changes to the alkaline side, with resulting deposition of calcium. A week later phosphatase is liberated by the osteoblasts; this causes deposition of calcium and phosphorus in the osteoid tissue.

The new material formed at the site of the fracture is known as *callus* on account of its hardness. In the later stages it may become calcified, but at first it is osteoid in character. Some of it is *external*, ensheathing the broken ends like solder; some is *intermediate*, forming a direct union between the fractured surfaces; some is *internal*, filling the marrow cavity. The

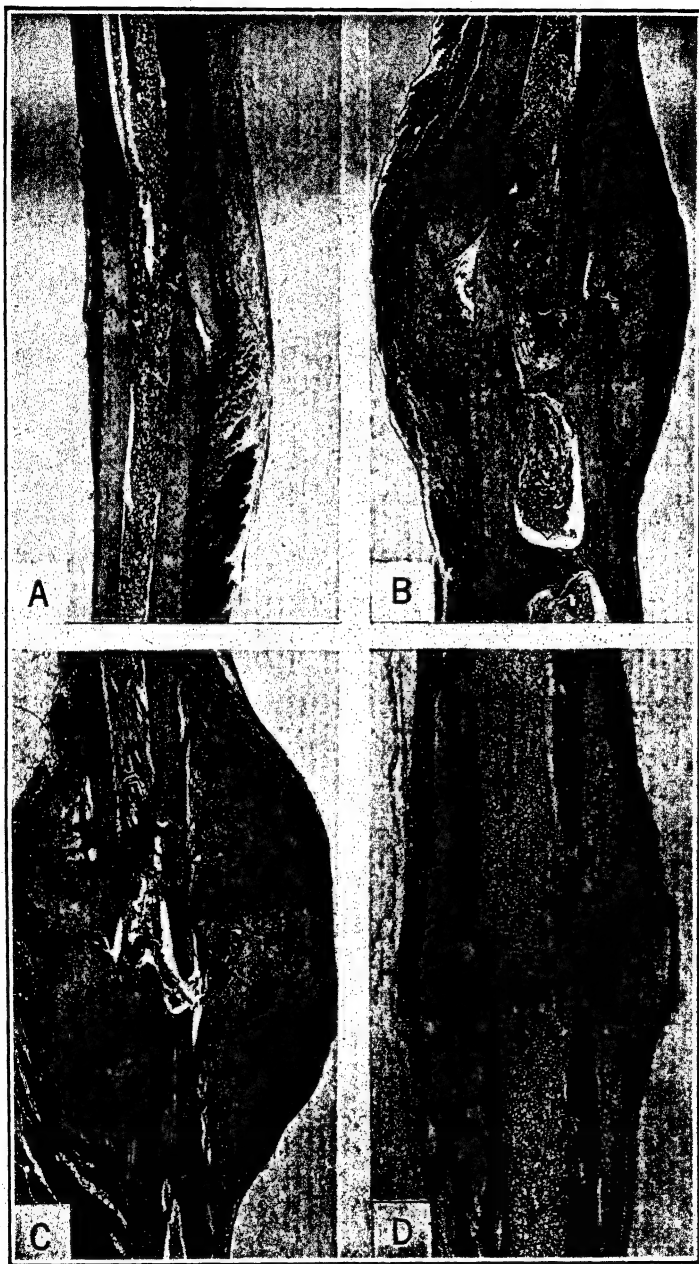


FIG. 508.—Healing of experimental fractures.  $\times 14$ . *A*, Three days (subperiosteal osteoblasts); *B*, seven days (osteoid); *C*, fifteen days (abundant callus); *D*, six weeks (diminished callus being converted into bone). (Boyd, *Surgical Pathology*, courtesy of W. B. Saunders Company.)

internal and external callus is removed by osteoclasts, and the bone undergoes a process of molding which goes on for months, and results in a rearrangement of the lamellæ to meet the new stresses. If the gap between the fragments is not bridged by osteogenic cells in a certain time, fibroblasts will fill the gap with fibrous tissue, the matrix of which has no special affinity for calcium salts (non-union or fibrous union).

**Fate of a Bone Graft.**—When a piece of bone is transplanted to another position the greater part of it dies. Dead bone can be easily recognized under the microscope from the shrivelled appearance of the bone cells and the fact that large numbers of the lacunæ are empty. The part of bone bathed by the body fluids remains alive, *i. e.*, the surface, the lining of the medullary cavity, and the Haversian canals. The cells in these places are osteoblasts, so that osteoblastic activity is soon apparent. But much more striking, especially in the earlier stages, is bone removal. New vessels from the surrounding tissue grow along the Haversian canals, so that the bone becomes revascularized and is at the same time absorbed. Multinucleated osteoclasts also attack the graft, and many foreign body giant cells may be formed. The removal of the graft is gradually brought about by the two great processes already studied, *i. e.*, vascular absorption and osteoclastic activity. In the course of six months if the graft has no function to perform it is merely represented by an atrophic mass of fibrous tissue. On the other hand if it becomes a functioning structure, as when it is in continuity with another bone, osteoblastic activity is combined with absorption, and gradually it becomes the dominant process. The graft may finally become converted into living healthy bone. If the graft is taken from an animal of another species, none of the osteoblasts will survive.

### ACUTE OSTEOMYELITIS

The term osteomyelitis indicates inflammation of bone and bone-marrow. But it is really an inflammation of the soft parts of bone, *i. e.*, the contents of the medullary cavity and the Haversian canals, together with the periosteum. It is a boil in a bone. The calcified portion takes no active part in the process, but it suffers secondarily from the loss of blood supply, and a greater or less portion may die.

**ETIOLOGY.**—Osteomyelitis may be: (1) hematogenous, or (2) non-hematogenous in origin. In the non-hematogenous form the infection may come (*a*) from without, or (*b*) by extension. In *children* and adolescents (those with growing bones) osteomyelitis is due to a hematogenous infection. The common infecting organism is *Staphylococcus aureus*. Next in frequency come *Staphylococcus albus*, *Streptococcus pyogenes*, *Pneumococcus* (especially in babies and young children), *Bacillus coli*, and *Bacillus typhosus*. The staphylococcus often enters the blood stream through the skin, and it is common to find a healing boil if the whole body is carefully examined. In other cases the throat, teeth, and tonsils may be suspected. *Trauma* is often given as a predisposing cause, but this is so common in a young boy that it is difficult to be sure of its significance.

In *adults* hematogenous infection is rare. When it does occur the disease is much less acute. Infection is most likely to be introduced from without,

as in a compound fracture, gunshot wound, etc. In children also the infection may be local in origin, as in osteomyelitis of the mandible from an infected tooth, or inflammation of the mastoid process from middle-ear suppuration.

**SYMPTOMS.**—Acute hematogenous osteomyelitis is a disease of children, commonest in boys in the second decade. It is a disease of growing bones, rarely seen in the adult. It commences with the signs of an acute infection, *i.e.*, chills, high fever, rapid pulse, leucocytosis, and positive blood culture. There is severe pain and tenderness at the end of one of the long bones, together with redness, swelling, and edema. Death may occur from septicemia or pyemia (endocarditis, abscesses in the kidneys, etc.), or if treatment is inadequate, the disease may become chronic. As the initial lesions are confined to the soft parts of the bone, there are no characteristic roentgen-ray changes in the earlier stages of the disease.

The above account applies to the disease before the days of chemotherapy. With the advent of antibiotics osteomyelitis has become a medical rather than a surgical disease. The description which follows applies to untreated cases.

**LESIONS.**—In this description of the lesions it is presumed that we are dealing with the hematogenous osteomyelitis of children. The bones most often affected are the femur and tibia (much exposed to trauma and strain), followed by the humerus. The infection starts in the metaphysis—the part of the shaft which borders on the epiphyseal line in a growing bone.

The initial lesion is a focal suppuration abscess of the cancellous bone at the end of the shaft. Infection *spreads* rapidly in two directions: (1) along the medullary cavity, and (2) outward to the cortex. Pus is formed beneath the periosteum and lifts that membrane from the bone, at the same time making its way along the outside of the shaft. Many of the vessels are found to be thrombosed, and the septic thrombi form the chief menace

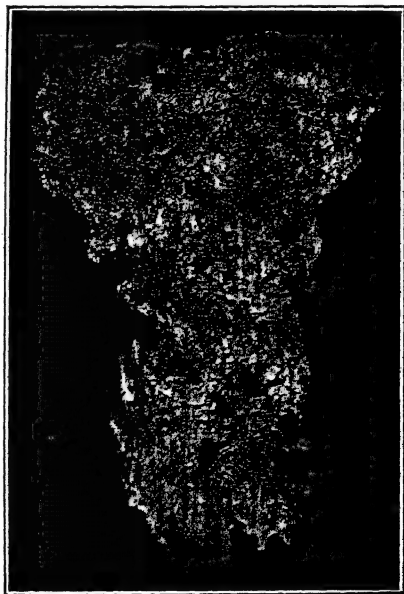


FIG. 509.—Osteomyelitis of upper end of tibia showing new bone formation and cloacae.

of osteomyelitis, namely, the formation of pyemic abscesses throughout the body. The denuded surface of dead bone has an opaque white appearance and does not bleed when scraped. The fatty tissue of the marrow is destroyed and is converted into an oily pus. The *adjacent joint* is often filled with a sterile serous effusion. Sometimes the infection may pass to the epiphysis, perforate the articular cartilage, and invade the joint, setting up a suppurative arthritis.

The dead bone becomes separated from the living by the action of osteoclasts, forming a *sequestrum*, which can be lifted out freely when it is exposed at operation. But in the meantime the periosteum is not inactive. Although it is separated from the bone, some of the cells of the osteogenic layer usually survive, and when the acuteness of the infection is past these osteoblasts lay down new bone over the sequestrum in the form of a *new case* or *involucrum*. The involucrum is perforated here and there by *cloacæ* or sewers through which passes the pus produced by the irritation of the dead bone. (Fig. 509.) Nature is unable to deal with this state of affairs, and the dead shaft remains locked up within the rigid involucrum without any change of being absorbed.

*Osteomyelitis of the spine* usually commences in the neural arches of the vertebræ, although in the cervical region it is more likely to start in the vertebral bodies. When it begins in the neural arches the pus spreads backward, when it begins in the bodies it spreads forward, and may cause a retropharyngeal abscess. Death is likely to result from septic meningitis.

**THE RELATION OF SYMPTOMS TO LESIONS.**—The chief symptoms of acute osteomyelitis is pain and tenderness at the end of one of the long bones. This is due to the extreme tension within the unyielding bone caused by the violent inflammation. The septicemic and pyemic symptoms are explained by the readiness with which the infected material and septic thrombi pass from the sinusoids of the marrow into the veins and the general circulation.

**CHRONIC OSTEOMYELITIS.**—If acute osteomyelitis is not adequately treated, *i.e.*, if the focus of suppuration is merely incised, the condition may become chronic and drag on until the patient dies of amyloid disease. But it may be more or less chronic from the beginning, with no definite history of an acute attack. Such a condition is known as a *Brodie's abscess*, a chronic circumscribed focus of suppuration at the upper end of the tibia, lower end of femur, upper end of humerus, and occasionally elsewhere. During periods of quiescence there is a small cavity surrounded by dense bone and containing a little serous fluid, but during periodic exacerbations the cavity is filled with pus from which staphylococci may be isolated. *Typhoid osteomyelitis* is a chronic infection which usually appears about two months after the acute illness, but there may be an interval of several years. The bacilli have been isolated twenty years after the original infection. The upper end of the tibia, the ribs and the sternum are the common sites.

**NON-SUPPURATIVE EPIPHYSITIS.**—Of recent years a group of cases has come to be recognized, in which there is a quiet necrosis of the epiphysis of a bone in young children. The best recognized form is that known as *Legg-Perthes' disease*, an osteochondritis deformans affecting the head of the femur, but *Köhler's disease* of the scaphoid and *Kienböck's disease* of the os lunatum belong to the same group. The center of ossification of the head of the femur, scaphoid, etc., is broken down and necrotic, so that several small sequestra may be formed, but without any pus. The condition is probably the result of a very low-grade infection, which clears up in time, so that complete spontaneous recovery is the rule. In Legg-Perthes' disease there is a remarkable flattening of the head of the femur, the neck being stunted and thick, giving a roentgen-ray picture from which a diagnosis can readily be made. Limp is the chief symptom, and there is usually little or no pain.

## TUBERCULOSIS OF BONE

Tuberculosis of bone is a chronic osteomyelitis occurring in early life, displaying an excess of bone destruction over bone formation, yet with a



tendency toward limitation of spread and spontaneous healing. The disease begins in spongy bone, and is commonest in the vertebræ, the small bones of the hands and feet, and the ends of the long bones including both metaphysis and epiphysis. As in the case of acute osteomyelitis, the region of the knee (lower end of femur and upper end of tibia) is a common site. There may be more than one focus; in the vertebral column this is the rule, not the exception. The infection is usually hematogenous, being carried to the spongy bone by the blood stream from a distant focus in lung, lymph nodes, etc., although occasionally no evident focus can be found. Trauma probably plays a part in inducing the bacilli to settle down, as can be shown experimentally, but the trauma must be mild. A severe injury such as a fracture calls forth such a rapid reparative reaction that the bacilli have no chance to establish themselves. Sometimes the infection spreads from a joint to the epiphysis by way of the perivascular lymphatics. Bone and joint tuberculosis are often associated; the primary lesion may be in either structure.

LESIONS.—The lesions are of two main types: (1) There may be little or no caseation, but an abundant formation of soft tuberculous granulation tissue. (Fig. 510.) This exerts an erosive action, as a result of which the Haversian canals are enlarged and the outer and inner surfaces of the bone are eaten away. Osteoclasts assist in the work of destruction; but it is not



FIG. 510.—Tuberculous granulation tissue causing erosion of bone. Several giant cells can be seen.

a wholesale destruction. Branching trabeculæ of bone are left, the interspaces being filled with granulation tissue. This is a process of rarefaction or osteoporosis to which the name of *caries* is given. (2) There may be marked softening, destruction of bony trabeculæ, and caseation, which may be followed by the formation of tuberculous pus and a cold abscess. This type of lesion is characteristically seen in tuberculosis of the vertebræ. Although the lesions of tuberculosis are essentially destructive there may be a limited amount of osteosclerosis and formation of new bone. The periosteal osteogenic activity characteristic of osteomyelitis is never seen in tuberculosis, unless a septic element has been superadded.

The infection may spread down the medullary cavity so that most of the shaft is involved. It may spread through the epiphyseal cartilage, or if it starts in the epiphysis it may perforate the articular cartilage and invade the joint; the articular cartilage may be completely separated from the



underlying bone. It may spread to the periosteum, where it forms a subperiosteal abscess. The soft parts then become involved, with the formation of a cold abscess which discharges through a sinus on to the skin.

*Tuberculous dactylitis* is a condition in which a metacarpal or one of the phalanges develops a fusiform swelling as a result of diffuse involvement of the medulla. The interior of the shaft is absorbed and new bone is laid down on the surface by the periosteum, so that the shaft appears to be expanded.



FIG. 511.

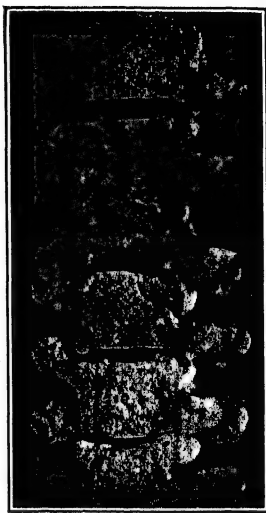


FIG. 512.

FIG. 511.—The central form of tuberculosis of the spine. The body of one vertebra is destroyed and collapsed, causing backward curvature of the spine.

FIG. 512.—Peripheral form of tuberculosis of the spine with surface involvement of many of the vertebral bodies.

*Tuberculosis of the Vertebrae*.—This is also known as Pott's disease of the spine. The vertebrae are the commonest bones affected by tuberculosis. The disease occurs especially in young children, and usually begins in the center of the body of a vertebra which is supplied by a branch of the posterior spinal artery. Discrete lesions are often present in several adjoining vertebrae. The center of the bone becomes caseous and the disease spreads to and destroys the intervertebral discs, but spares the transverse processes, spines, and articular processes. The destruction of the discs is of special importance, because in secondary carcinoma of the vertebrae which often presents a radiological picture very similar to that of tuberculosis, the discs are hardly ever involved. The bodies collapse in front, while the spines remain intact behind, so that an acute curvature develops with its convexity pointing backward. (Fig. 511.) In the rather rare *peripheral* form of adults the disease is confined to the anterior surface of the vertebrae, an area supplied by branches from the intercostal arteries; there is little or no deformity, but a large number of vertebrae may be involved. (Fig. 512.)

In children there is usually evidence of pressure on the cord. This is not due to the angling of the spine, but to the formation of tuberculous granulation tissue or to an accumulation of pus under the posterior common ligament which presses on the cord. It is remarkable how even severe pressure symptoms such as paraplegia may clear up when the weight is taken off the spine.

A *cold abscess* often develops and this may trek in almost any direction, although it is unable to travel directly backward owing to the posterior common ligament. It soon escapes at the sides of the vertebræ, and is then free to travel at will. In the *cervical* region it may form a retropharyngeal abscess or may appear at the side of the neck. In the *dorsal* region it may spread along a rib; when it comes to the surface it is very liable to be mistaken for primary disease of the rib unless the spine is carefully examined. In the *lumbar* region the pus enters the sheath of the psoas muscle, and passes down as a psoas abscess into the iliac fossa and under Poupart's ligament; it may then point at the saphenous opening or may pass down the thigh as far as the popliteal space. The pus may enter the sheath of the iliacus instead of the psoas; it will then point above Poupart's ligament. In any of these sites mistakes in diagnosis are frequent. When the abscess discharges on the surface a mixed infection develops, and the clinical picture changes very much for the worse with hectic temperature and rapid wasting. Amyloid disease may now develop, or the patient may die of general miliary tuberculosis.

The *course* of the disease varies. As the spine is seldom at rest there is a strong tendency to progression. If the patient is kept absolutely at rest on his back under the best hygienic conditions an astonishing recovery may follow with firm fibrous union between the vertebræ.

## SYPHILIS OF BONE

Syphilitic disease of bone is an inflammation, an osteitis, just as tuberculosis is a special form of inflammation. It differs from tuberculosis in the following respects: (1) it affects the diaphysis of long bones rather than the articular ends, (2) the joint is seldom involved, and (3) osteosclerosis with new bone formation is much more prominent than osteoporosis or rarefaction. The bones most commonly affected are the tibia, sternum, cranium, and the bones of the face, especially the nose and palate. The disease may be of the acquired or congenital form. The lesions may appear in the earlier or the later stages. In the earlier stages there is likely to be a periostitis; in the late stages gummatous formation is not uncommon. The two common manifestations of bone syphilis are the periosteal node and diffuse osteitis.

**THE PERIOSTEAL NODES.**—Clinically this is the characteristic lesion. It takes the form of a localized, firm, painful, tender swelling most frequently seen on the subcutaneous border of the tibia. In congenital syphilis the tibia may present a marked forward curve, a condition known as "sabre-blade" tibia. The spirochetes appear to settle in the deeper vascular layer of the periosteum, and an abundant cellular granulation tissue is formed around the vessels not only in the periosteum but also in the mouths of the Haversian canals. The tension produced by this new tissue within the bony canals is responsible for the nocturnal boring pains alluded to by the Psalmist.

**DIFFUSE OSTEITIS.**—In this form, also called diffuse osteoperiostitis, the greater part of the shaft or the entire bone is involved from the periosteum to the medulla

and from one articular cartilage to the other. New bone is laid down by the osteoblasts under the periosteum causing marked uniform thickening of the shaft, on the walls of the dilated Haversian canals causing greatly increased density of the bone, and in the medulla causing obliteration of that cavity. The entire bone is now dense and heavy.

**SYPHILITIC EPIPHYSITIS.**—This is so characteristic a feature of congenital syphilis in the newborn that a convenient method of diagnosing that condition at autopsy is to cut open the lower end of the femur or the upper end of the tibia and inspect the epiphyseal line. The normal line is thin as an edge of paper and pearly-gray, but in syphilitic epiphysitis it becomes broad, irregular, toothed, and of an opaque yellowish-white color. (Fig. 513.) When examined with a magnifying glass it has a granular appearance not unlike mortar. Microscopically it is seen that the process of ossification has become gravely disordered, irregular lines of cartilage extending into the diaphysis and thus causing marked widening of the epiphyseal line. In severe cases the place of the cartilage is taken by syphilitic granulation tissue, in which necrosis and caseation take place. It is evident that such a line, instead of uniting the epiphysis and diaphysis, merely forms a space which separates them, and the epiphysis may become detached either spontaneously or as the result of trauma, giving rise to syphilitic pseudoparalysis. The roentgen-ray appearance is diagnostic. Anti-syphilitic treatment soon brings about reunion and normal ossification.



FIG. 513.—Syphilitic epiphysitis. The epiphyseal line of the lower end of the femur is broad and dark.

**SYPHILITIC DACTYLITIS.**—This is another manifestation of congenital syphilis in children. There is a diffuse infiltration of the marrow of one or more of the phalanges, with expansion and erosion of the medullary cavity and a formation of new periosteal bone on the surface. The affected digit presents a spindle-shaped swelling, which is easily mistaken for tuberculous dactylitis.

**BONES OF THE FACE.**—Gummatous destruction of the bones of the nose and the hard palate are common in *congenital syphilis*. The bridge of the nose falls in at the root (saddle-nose), and there may be a large perforation in the palate. The latter condition is also seen in the late stage of *acquired syphilis*.

**EOSINOPHILIC GRANULOMA.**—This is a painful inflammatory lesion often in the skull, sometimes in a rib or long bone, occurring in children and young adults. It may be mistaken clinically for osteomyelitis, tuberculosis and Ewing's tumor. The lesion is soft, expands the bone, and consists of histiocytes, numerous eosinophilic polymorphonuclears, and sometimes giant cells arranged around cholesterol crystals. In spite of the name eosinophils may not be numerous, especially if the tissue is examined in the early proliferative or in the late healing stage. Lipoid cells are rare. The essential element in the lesion appears to be sheet-like collections of histiocytes. Farber suggests that the lesions are of the same basic character as those of Schüller-Christian's disease, so that the condition may be classed with the reticulo-endothelial granulomas. In eosinophilic granuloma they are often confined to a single bone, and the distinctive feature is an intermingling of large numbers of eosinophils with the histiocytes, whereas

in Schüller-Christian's disease the lesions are more widespread, and the histiocytes become loaded with lipid. Letterer-Siwe's disease, in which the lesions are distributed throughout the skeleton and the soft parts, especially the lymph nodes, belongs to the same group. In eosinophilic granuloma the health remains good, and the disease is generally of short duration and self-limited.

## TUMORS OF BONE

In studying the difficult subject of bone tumors it is desirable to determine the constituents of the bone from which the various tumors arise. In many cases this is possible; in some it is difficult or impossible. Bone is a connective tissue which happens to be impregnated with lime salts. Anatomically it consists of periosteum, bone and bone-marrow, while at each end of the growing bone there is epiphyseal cartilage. The periosteum consists of *fibrous tissue* and *osteoblasts*. The bone contains adult *bone cells* which are end-products incapable of proliferating and giving rise to a tumor, *osteoblasts*, and *osteoclasts*. The marrow consists of *marrow cells*, which need not be particularized further, and reticular or *reticulo-endothelial cells*. In general terms, which will be subject to subsequent analysis, it may be said that the periosteal fibroblasts may give rise to fibrosarcoma, the osteoblasts to osteoma or osteogenic sarcoma, the osteoclasts to giant-cell tumor, the cartilage cells to chondroma and chondrosarcoma, the marrow cells to multiple myeloma, and the reticular or reticulo-endothelial cells to Ewing's tumor. It is convenient to consider the innocent and malignant tumors separately.

In the introduction to their fine monograph on "Tumors of Bone," Geschickter and Copeland point out that it is not sufficient to consider the constituents of adult bone; the development of bone must also be taken into account. The development of the skeleton is never really complete, for transition forms between the different tissues persist in certain places at all ages, and may serve as the starting-point for tumors. Most primary bone tumors, they consider, arise in connection with such transitions in growth. In the lowest vertebrates the skeleton consists of connective tissue, higher in the scale, cartilage takes the place of connective tissue, and finally the cartilage gives way to bone. This processional process is repeated in the human embryo, whose skeleton first consists of connective tissue, later of cartilage, and finally of bone. In the case of bones which are developed in membrane, *e.g.*, most of the bones of the skull, there is direct ossification in the primitive connective tissue, the connective-tissue cells becoming changed into osteoblasts which lay down bone. Such bones are not liable to the development of primary tumors. In the case of bones developed in cartilage the process is much more complex. The primitive connective tissue is first changed into fetal cartilage composed of small round cells; this develops into adult cartilage which becomes calcified; the calcified cartilage is removed by giant-cell osteoclasts, canalized and vascularized; finally permanent cancellous bone is laid down. This process goes on actively on both sides of the epiphyseal line, up to adult life on the shaft side, much later in life in the epiphyses. The embryonic connective tissue which has the ability to form both cartilage and bone persists in various places, and is especially abundant in the neighborhood of joints. If these facts be borne in mind, and if it be realized that developmental processes continue well into adult life, the skeletal and age distribution of tumors and the possible types which may occur will be better understood. Geschickter

and Copeland use a histiogenetic basis for their classification of bone tumors. "It is in delayed developmental steps in the persisting primitive connective tissue of the skeleton and in conjunction with subsequent histiogenic steps, after the cartilage of the skeleton has been formed, that practically all primary bone tumors take origin."

**Innocent Tumors.**—**OSTEOMA.**—Most formations of new bone are not true tumors, but outgrowths from the surface known as *exostoses*; they are usually caused by the irritation of trauma. A *compact osteoma* is an ivory-hard tumor of the skull probably formed by the periosteal osteoblasts. A *cancellous osteoma* may be regarded as a bone in miniature, for it possesses its own epiphyseal cartilage by virtue of which it grows as long as the growth of the skeleton continues. It is therefore also known as an osteochondroma. Some writers call this tumor an exostosis. It arises from the end of one of the long bones, probably from a segment of epiphyseal cartilage, and the tumor is covered by a cap of cartilage until ossification is complete. As the bone grows in length, the tumor becomes displaced from the region of the epiphyseal line. An osteoma may grow from the bones of the face and attain a large size.

**OSTEIOD OSTEOMA.**—This is a benign tumor of slow growth, commonly located in the tibia or femur, and develops between the ages of ten and twenty-five. Pain, together with swelling and tenderness, lead to a mistaken diagnosis of bone abscess or chronic osteomyelitis. The tumor is small, but it is surrounded by much new bone, or rather by calcified osteoid tissue. The lesion is at first cellular, later osteoid, and is finally calcified atypical bone. The x-ray picture is characteristic, consisting of a central rarefied area, the tumor, surrounded by a dense area of sclerosis.

**FIBROMA.**—Fibroma of bone is rare. It grows from the outer layer of the periosteum, usually in connection with the superior maxilla or the posterior wall of the nasopharynx where it forms a fibrous polypus.

**CHONDROMA.**—Cartilaginous tumors may arise from the epiphyseal cartilage or from the cartilage which precedes the developing bone, islands of which may remain unabsorbed. They occur during the growing period, and are commonest in the short bones of the hands and feet where they may be multiple. Single chondromas of large size may grow from the scapula, pelvis, neck of femur, and other bones. These single tumors often undergo myxomatous and cystic degeneration, and are then liable to show malignant change into a *chondrosarcoma* especially when interfered with. It may be easier to detect this change from the clinical behavior and the gross appearance at operation (invasion, etc.) than from the microscopic structure. Invasion of the veins and metastases to the lungs confirms the malignant character of the change. A chondroma may grow on the surface or the interior of the bone. The latter form, known as an *enchondroma*, may cause expansion of the shaft, and when combined with cystic degeneration may give a roentgen-ray picture closely simulating that of giant-cell tumor. The condition known as multiple cartilaginous exostoses or chondrodysplasia is considered in connection with the bone dystrophies.

**GIANT-CELL TUMOR.**—This condition has in the past been called giant-cell sarcoma and myeloid sarcoma under the mistaken belief that the tumor was malignant. A more modern term is *osteoclastoma*, i. e., a tumor

of osteoclasts. It is locally destructive and may be invasive, but it does not give rise to metastases nor kill the patient, although it shows a fairly marked tendency to local recurrence. In actual practice it is well to associate the giant-cell tumor with the malignant tumors of bone, for it is from them that the differential diagnosis has to be made, although a central chondroma may sometimes give a similar roentgen-ray picture. In rare cases a giant-cell tumor may become malignant and metastasize to the lungs. When the benign tumor is removed by curettage a smooth-walled cavity should remain. If the tumor recurs there is danger of malignancy, and amputation should be considered.

The tumor develops in children and young adults, usually before the age of thirty years. It occurs principally at the ends of long bones, usually originating in the epiphysis, occasionally in the diaphysis. The epiphyseal location is of value in differentiating the lesion from bone cysts in the x-ray film. The common location is the knee (lower end of femur, upper end of tibia), but it may occur in any bone developed in cartilage. The bones developed in membrane (cranium) are free. The reason for this will soon be apparent. The center of the bone is expanded, and the cortex often reduced to a mere shell, so that a spontaneous fracture may first attract the attention of the patient to the condition which is usually painless. Fairly thick bone trabeculae are left traversing the cystic lesion like beams supporting a crumbling building. This arrangement, best seen in the dried and macerated specimen from which the soft tissue has been removed or in the operating room when the soft parts are curetted away, is responsible for the soap-bubble appearance (see below). The *roentgen-ray picture* is highly characteristic, and from it a diagnosis can usually readily be made. It shows a rarefied, multicystic, or trabeculated appearance as if the mass was composed of large bubbles, thinning of the cortex, and sharp limitation of the lesion from the surrounding bone and soft parts.

The *gross appearance* is that of a soft, dark red, hemorrhagic mass, sometimes with yellow areas. The material can be curetted away, and this is the usual form of treatment. Many cases respond well to radiation, but others do not. Cyst formation may occur in the center and the cyst may be filled with blood. There may be great expansion of the end of the bone. (Fig. 514.) *Microscopically* the tumor is composed of three types of cells: spindle-shaped cells, round cells, and giant cells. (Fig. 515.) The round cells are more numerous during the period of active growth. Predominance of the spindle cells indicates quiescence of the growth and a tendency to healing; they are the cells which constitute the lesion in osteitis fibrosa. In determining the neoplastic nature of the lesion attention must be paid not to the giant cells but to the cells of the stroma (round and spindle). These must show neoplastic characters to justify a diagnosis of giant-cell tumor (Aegerter). Giant-cell tumor of the vertebræ, which responds very favorably to even partial removal, is composed largely of spindle cells. The giant cells are large multinucleated cells of the osteoclast type. They may be numerous in one part, scanty in another. They differ from the rather similar cells of a granuloma in that the numerous small nuclei are situated toward the center of the cell and not around the periphery, and they are quite different from the tumor giant cells of an

osteogenic sarcoma, which contain a few large irregular nuclei. The tumor is highly vascular, so that hemorrhage is frequent.

The *epulis* (*epoulis*, upon the gums) is a tumor in the gum growing in relation to the teeth. There are two forms: the giant-cell epulis, which is the common type and is similar in nature to the giant-cell tumor of bone, and the fibrous epulis which is similar in character to osteitis fibrosa. Epulides occur in children and young adults, and arise from the alveolar dental periosteum of the deciduous teeth (canine and bicuspid). They hardly ever occur at the site of the molars, which make only one (permanent) appearance. The growth is outward, often between the teeth, and does not invade the bone. In addition to the epulis, a central giant-cell tumor of bone may occur in the lower jaw between the symphysis and the mental foramen.



FIG. 514.—Giant-cell tumor of the upper end of the tibia. The material expanding the end of the bone is soft, red, and resembles blood clot.

The nature of the giant-cell tumor has long been a matter of dispute. By some it is considered to be inflammatory rather than neoplastic in nature, the giant cells being regarded as foreign body giant cells. The most satisfactory way of regarding the lesion, as suggested by Geschickter and Copeland, is to consider giant-cell

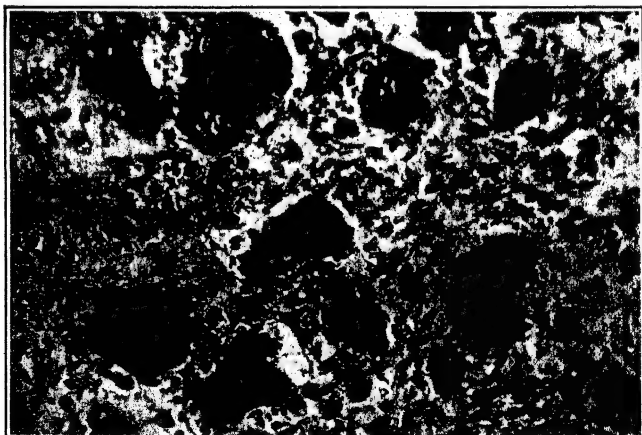


FIG. 515.—Giant-cell tumor of bone. The multinucleated giant cells are unusually numerous.  $\times 225$ .

tumor and osteitis fibrosa as two phases of a transition process in the histogenesis of permanent bone; the former is an active vascularizing phase, the latter a healing phase. In the formation of normal bone there is a canalization, vascularization, and final removal of calcified cartilage, a process in which osteoclasts and round and spindle cells similar to those of the giant-cell tumor play an active part. This process may overstep the bounds of normal activity and become neoplastic, giving rise to a tumor which may be called an *osteoclastoma*. If the process is restrained and only slightly destructive, the result will be localized osteitis fibrosa with the possible formation of a bone cyst. Trauma is probably a factor of importance in disturbing the blood supply to the growing part, but the relation of trauma to a tumor must always be subjected to critical scrutiny.

This view throws light on a number of the features of giant-cell tumor. It explains its age incidence, its localization at the growing ends of bones (including the epiphysis), and its relation to osteitis fibrosa. The giant-cell epulis arises in a similar manner. The shedding of the deciduous teeth is brought about by the action of giant-cell odontoclasts, and the tumor is an *odontoclastoma*. The fibrous epulis corresponds to osteitis fibrosa. In the skull giant-cell tumors of central character, as distinguished from the epulides, are confined to parts developed in cartilage, *i.e.*, temporal fossa, the part of the mandible between the symphysis and mental foramen which is developed from Meckel's cartilage, and the anterior part of the superior maxilla. The giant-cell tumors (xanthomas) of tendon sheaths may also be explained in this way. The calcified structures with the removal of which they are concerned are the sesamoid bones.

Stewart and others believe that the two processes are entirely distinct, and that the true osteoclastoma is a primary neoplasm unrelated to osteitis fibrosa. It is more sharply circumscribed than the giant-cell lesions of osteitis fibrosa and the rest of the skeleton is quite normal. The rare cases of malignant giant-cell tumor would rather support this view.

**Malignant Tumors.**—Malignant tumors of bone may be primary or secondary. Secondary tumors are carcinoma, and usually occur after middle age. They are far commoner than primary tumors, and should always be suspected in a case of bone tumor in the latter half of life. Primary tumors are sarcomatous in type, and for the most part occur during adolescence. There are three principal types: *osteogenic sarcoma* (by far the commonest), *Ewing's tumor*, and *multiple myeloma*. To these must be added *chondrosarcoma*, as well as a number of rare types. The giant-cell tumor has to be compared with the primary malignant tumors for purposes of clinical differentiation. Osteogenic sarcoma and Ewing's tumor occur chiefly in childhood and adolescence, giant-cell tumors are commoner in the third decade, and multiple myeloma generally occurs after the age of forty years. The site of election of osteogenic sarcoma is at the end of the long bones (metaphysis), giant-cell tumor at the epiphysis, Ewing's tumor in the shaft of the long bones, and multiple myeloma in the flat bones.

**OSTEOGENIC SARCOMA.**—This is the most common and the most malignant of bone tumors. It is a disease of the second and third decades (ten to thirty years), and is very rarely seen after the age of fifty years. It occurs at the end of the shaft (metaphysis) of the long bones, usually in the region of the knee (lower end of femur, upper end of tibia). Over 70 per cent of cases occur in the lower limb. The order of frequency is as follows: femur, tibia, humerus, pelvis, fibula. It hardly ever occurs in the forearm.



A history of trauma is common but not so constant or convincing as in Ewing's tumor. Nothing is more difficult than to judge the relationship of trauma to tumor. There is no relation between fracture and any form of bone tumor. Martland has pointed out that osteogenic sarcoma may develop in those whose bones have become highly radio-active. In a group of girls who died from the ultimate effects of swallowing highly radio-active substances while painting the dials of luminous watches, 27 per cent of the deaths were due to osteogenic sarcoma. It was calculated that in the year 3491 A.D. the skeleton of one of these girls would still be

giving off 185,000 alpha particles per second, each of these travelling at the rate of 18,000 miles per second.

The *gross appearance* depends on the stage. The first symptom is pain due to involvement of the sensitive periosteum, and this may precede the appearance of a tumor by weeks or months. When the tumor is well developed there is a fusiform mass at the end of the bone which fades away on to the shaft, giving a "leg of mutton" appearance. (Fig. 516.) At first the disease is confined to the bone, with involvement of the shaft, the medulla, and the periosteum, but in the later stages the periosteum is perforated with rapid dissemination of the growth in the soft parts. There is a coincident absorption and deposition of bone; the original shaft is absorbed, but tumor bone is laid down in the subperiosteal space by the osteogenic tumor cells. It is curious to note that the innocent giant-cell tumor is destructive (osteolytic), while the very malignant osteogenic

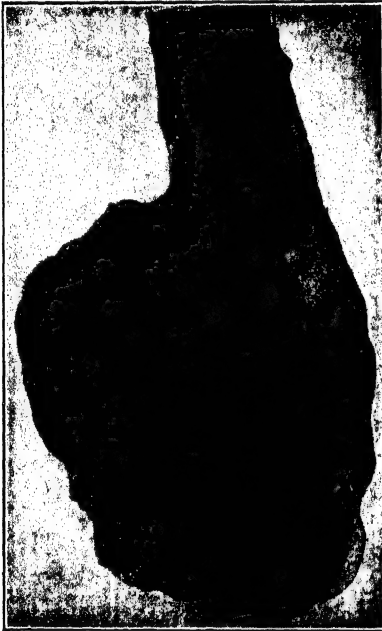


FIG. 516.—Osteogenic sarcoma of lower end of femur. The tumor has destroyed the shaft, and is both medullary and periosteal in distribution.

sarcoma forms new bone. This formation, however, is quite patchy, so that pathological fracture is likely to occur in the later stages. As the periosteum is lifted up from the bone by the tumor the vessels which enter the shaft from the periosteum are drawn out in parallel vertical lines, which form a scaffolding on which the new bone is laid down. Fine spicules are therefore found radiating outward from the central mass, and in the roentgen-ray picture these give a very characteristic "sun-ray" effect. The consistence of the tumor varies with the amount of bone formed, which may be much or little. The tumor may be very soft and sarcomatous, or firm and fibrous, or hard and bony. The usual color is gray, but the tumor may be highly vascular and hemorrhagic, and may present cysts filled with blood. Necrosis and softening are common.

The *microscopic picture* is extraordinarily varied, so that different cases differ widely, and in a single case there may be the same pleomorphism as is seen in glioblastoma multiforme of the brain. The *tumor cells* are osteoblasts, and three types may be seen. (Fig. 517.) (1) The most constant and characteristic form is a small spindle cell with hyperchromatic nucleus and poorly-defined cytoplasm. If the tissue is poorly fixed and stained, the cytoplasm may not be detected, so that the cells appear round, but an osteogenic sarcoma is never a round-cell tumor. (2) Other cells may be large and spindle-shaped or polyhedral. Mitoses are numerous in these cells. (3) Giant cells are often present. These may be tumor cells or foreign body giant cells. The tumor giant cells may be mononuclear or may contain a small number of large nuclei. The cells have a more irregular,



FIG. 517.—Osteogenic sarcoma showing the characteristically pleomorphic picture and a typical tumor giant cell.  $\times 300$ .

atypical, and neoplastic appearance than the foreign body giant cells. The latter are present when there is much bone destruction, and especially after an exploratory operation. The *intercellular substance* is as characteristic as the cells. It may be hyaline and fibrous, cartilaginous, myxomatous, osteoid, or osseous. Thus there may be formation of tumor bone. It is important for the pathologist to distinguish between tumor bone and true bone. Tumor bone is atypical and poorly formed, it blends with the stroma of the tumor, and it presents no bordering line of osteoblasts. When the stroma is largely fibrous, the sarcoma is of the sclerosing type. Calcium can be recognized by its dark blue color when stained with hematoxylin. If the blood vessels are very abundant, the tumor is said to be of the telangiectatic type. Invasion of the thin-walled vessels is common, and tumor cells may form the actual walls of the blood sinuses. The limb must therefore be handled with great gentleness. It is easy for metastases to be set up at the time of operation. Preliminary radiation of the tumor, by closing the vessels, diminishes this danger to a considerable degree.

*Spread* takes place mainly by the blood stream, as is natural from the vascular arrangement just described. Metastases usually occur in the lungs, but if the tumor emboli pass the pulmonary capillaries they may lodge in other organs. It is important to note that secondary growths in other bones are very rare; multiple bone tumors suggest Ewing's tumor in the young and multiple myeloma in the middle aged. The lymph nodes are sometimes involved, but any enlargement is usually inflammatory. There is marked local invasion, and when the periosteum is perforated the tumor spreads rapidly through the soft parts and causes stretching of the skin.

The prognosis is bad, four-fifths of the cases being dead five years after amputation (Coley and Pool). This means, however, that 20 per cent are alive at the end of that time. Features which make for a good prognosis are age (best between twenty and forty years, bad in first decade, extremely bad in osteogenic sarcoma complicating Paget's disease), low-grade malignancy (histologic), and peripheral site of lesion.

**EWING'S TUMOR.**—It was in 1920 that Ewing separated this tumor from the general group of bone sarcomas under the heading of endothelial myeloma. It forms about from 10 to 15 per cent of all malignant bone tumors (including giant-cell tumors in the total). The *clinical history* is characteristic, but is quite suggestive of osteomyelitis, a disease for which this condition is very often mistaken both by the clinician and the pathologist. The patient is usually between the ages of five and fifteen years, and the disease is quite rare above thirty years. There is often a history of trauma, followed shortly by pain, at first intermittent but later continuous, fever, and the appearance of a swelling. When the swelling is incised a soft necrotic cellular material is obtained which is easily mistaken for pus. The occasional occurrence of a moderate leucocytosis still further adds to the difficulties of diagnosis. The *roentgen-ray picture* shows diffuse involvement of the greater part of the shaft. There is a combination of bone formation and bone destruction; formation in the early stage, destruction later. The new bone on the surface may present a laminated appearance like the layers of an onion. One of the most striking characteristics of the tumor is its *response to radiation*; it may melt away just like a lymphosarcoma, only to return again later. This characteristic is of great diagnostic value.

There can be little doubt that some of the cases described in the literature as Ewing's tumor are really examples of metastatic growths. In most of these cases the diagnosis is based merely on a biopsy or roentgen-ray report, whereas no case can be finally accepted without a complete autopsy examination. This truth is strikingly demonstrated by a case reported by Willis in his monograph on the "Spread of Tumors," in which a patient presented all the clinical, radiological and pathological (gross and microscopic) evidence of Ewing's tumor, and yet proved at autopsy to be a case of adrenal neuroblastoma with widespread metastases in the bones.

The *gross appearance* is that of a very soft disintegrating tumor resembling brain tissue. The bones most often involved are tibia, humerus, femur, fibula, clavicle, and os calcis in that order. The tumor probably (but not certainly) starts in the medullary cavity, from which it invades and widens

the bone canals, expands the cortex, and irritates the periosteum to lay down successive layers of new bone. This is normal bone laid down parallel to the surface, not tumor bone laid down at right angles to the surface as in osteogenic sarcoma. The bulk of the tumor is subperiosteal, the medullary cavity becoming narrowed or even occluded by new reactive bone.

(Fig. 518.) Owing to the formation of new bone, pathological fracture is rare.

The *microscopic picture* is that of a round-cell sarcoma. The cells are round or polyhedral, very uniform in appearance (cellular monotony), with a round nucleus and indistinctly defined cytoplasm which stains poorly. (Fig. 519.) They are closely packed together, and are arranged in sheets or columns, but may be grouped



FIG. 518.—Ewing's tumor of humerus. The growth is characteristically diffuse, involving the entire shaft. There were secondary growths in several other bones. (From Boyd's Surgical Pathology.)

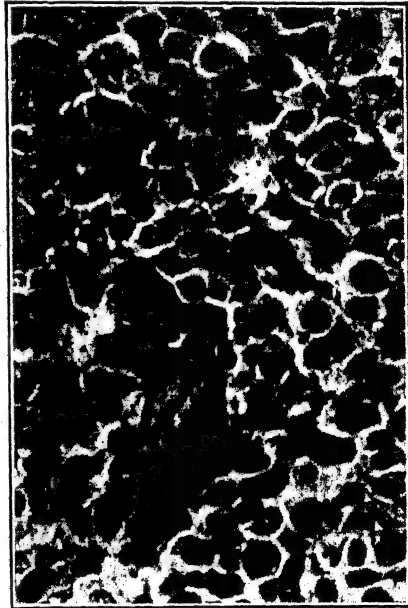


FIG. 519.—Ewing's tumor. Tumor cells are replacing the bone, fragments of which can be seen at left of picture.  $\times$  600.

around blood spaces so as to give an angio-endotheliomatous appearance. There is no intercellular substance, in striking contrast to osteogenic sarcoma. The microscopic appearance gives little help in determining the *nature of the tumor*. Ewing originally called it an endothelial myeloma, in the belief from the occasional peritheliomatous arrangement that it arose from the perivascular endothelium. Other workers do

not agree with this. As suggested at the beginning of the section on Bone Tumors, it may be a reticulum-cell sarcoma arising from the reticulo-endothelium of the marrow. For the present it is best to use the non-committal name of Ewing's tumor.

*Spread* occurs within the shaft both longitudinally and transversely by means of the bone canals, which in decalcified sections are seen to be filled with tumor cells. Distant spread occurs to the lungs, lymph nodes, other organs, and other bones. The bone metastases are of the greatest importance in differential diagnosis. They are hardly ever seen in osteogenic sarcoma. In multiple myeloma there is usually multiple involvement of bones when the patient is first seen, but in Ewing's tumor the patient comes with a single tumor, the secondary growths not developing for several months. These growths are commonest in the skull, vertebræ, sternum, scapula, and ilium, *i. e.*, the flat bones containing red marrow. The *prognosis* is very bad, although the disease may sometimes be held in check for several years by means of radiation.

**MULTIPLE MYELOMA.**—This highly malignant disease, which is really a marrow tumor rather than a tumor of bone, used to be regarded as a rarity, but the incidence has risen sharply owing to an increased awareness of the condition. The *clinical features* are pain and tenderness in the bones, weight loss, weakness, and a tendency to bleeding. The age incidence is noteworthy, nearly all the cases occurring over the age of forty. Marrow aspiration shows typical plasma cells, and the presence of rouleaux formation in the blood smear may suggest the diagnosis to the hematologist. The sedimentation rate is increased. Hyperglobulinemia is a characteristic feature, the globulins being probably produced by the plasma cells. Bence-Jones protein is present in the urine in under 50 per cent of the cases: a protein appears as a cloud when the urine is heated to 55° C., disappears at 85° C., but reappears on cooling. This represents the abnormal globulins present in the blood. There is an inverse relationship between the hyperglobulinemia and the proteinuria, for when the abnormal protein escapes in the urine it does not accumulate in the blood. Renal insufficiency is common, especially in the advanced cases, owing to obstruction of the tubules by casts of Bence-Jones protein with subsequent tubular atrophy (Fig. 520.) There is marked secondary anemia due to replacement of the marrow by tumor cells.

The most striking feature is the multiplicity of the lesions, as indicated by the name. The flat bones containing red marrow are first involved, *i. e.*, sternum, ribs, vertebræ, skull, and pelvis; lesions may appear later in the long bones. In rare cases there may be a diffuse myelomatosis without the formation of definite tumor nodules. It is not possible to say with certainty if the lesions are primarily multiple or if one is primary and the others secondary. The condition is comparable with lymphatic leukemia, in which the bone-marrow throughout the body is involved. Indeed, Jackson and his associates consider that multiple myeloma should not be regarded as a bone tumor, but as a disease of the blood-forming organs like leukemia, for the lymph nodes as well as the marrow may be involved. Some of the cases show atypical amyloidosis. The amyloid is atypical because it often fails to give the usual metachromatic staining

reactions for amyloid, and because it occurs in unusual situations such as skin, mucous membranes, tongue, heart, etc. It is possible that the abnormal blood proteins may serve as the mother substance of the amyloid proteins.

The *roentgen-ray picture* is usually characteristic. The bone lesions are purely destructive and they are localized, so that radiologically they appear as round, punched-out, clear-cut areas in a number of bones. Occasionally there is merely diffuse decalcification without any localized lesions. Owing to the rarefaction the cortex may be destroyed, so that pathological fractures are very common. The effect of radiation is similar to that in Ewing's tumor and lymphosarcoma. The lesions melt away marvellously but soon reappear.

The *gross appearance* is that of soft gray tumors of the marrow, which are at first localized and produce marked destruction of the bone. (Fig. 521.) It is a pure rarefying lesion with no formation of new bone. It may be noted, however, that spontaneous fractures heal readily and with good callus formation. Later the entire marrow cavity is filled with gray or red tumor tissue. *Microscopically* the picture resembles that of Ewing's tumor, but the cytology is not quite so uniform. The cells are round or polyhedral, are arranged diffusely, and there is no intercellular substance. The tumor is composed of plasma cells, although these differ from the classic plasma cell in not showing the characteristic coloration with the Unna-Pappenheim stain, the nucleus is larger, and there is seldom a perinuclear halo. (Fig. 522).

*Spread* is principally to the other bones. Metastases to the internal organs, especially the liver and spleen, are not common. The spleen may be enlarged even without metastases. Curiously enough, metastases are almost never found in the lungs.

**CHONDROSARCOMA.**—This tumor usually arises as a malignant development of a chondroma. Invasion of the surrounding structures and of veins is often a better indication of malignancy than the microscopic appearance. Usually, however, the regular arrangement of cartilage cells is lost, and the growth is much softer and more cellular in character than



Fig. 520.—Bence-Jones protein in kidney.  $\times 150$ .

the benign chondroma. Lung metastases are due to the frequent invasion of veins.

**SOLITARY PLASMACYTOMA.**—This is a rare tumor which may occur primarily in bone or in the upper air passages. As a rule, it is of only local malignancy, and is amenable to local removal or to operative treatment. In bones the plasmacytoma is usually multiple, and then constitutes one form of multiple myeloma.

**PERIOSTEAL FIBROSARCOMA.**—This is a rare tumor arising from the outer fibrous layer of the periosteum and not involving the bone itself. It is a firm white mass consisting of spindle cells, and is less malignant than the osteogenic sarcoma. It is not a true bone tumor, and its relation to bone is quite fortuitous.

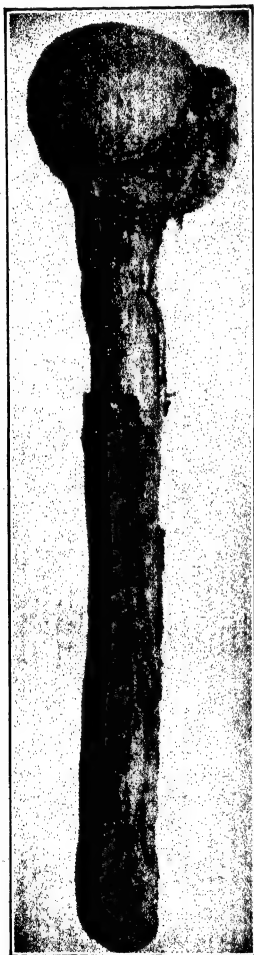


FIG. 521. — Multiple myeloma. Numerous punched-out cavities in the shaft of the humerus. (Kindness of Dr. H. M. Vango, from Boyd's Surgical Pathology.)

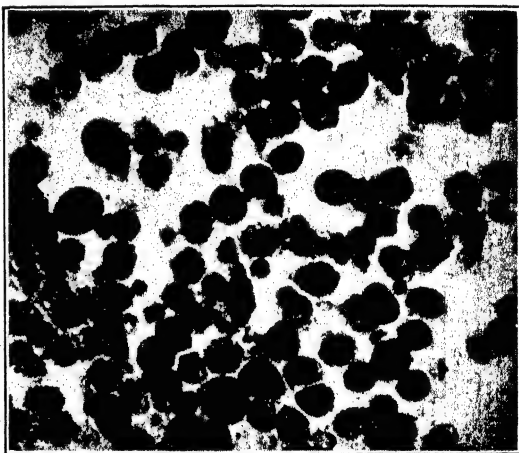


FIG. 522. — Plasma cell myeloma.  $\times 500$ .



FIG. 523. — Secondary carcinoma of bone.  $\times 250$ .

**RETICULUM-CELL SARCOMA.**—This rare bone tumor usually occurs before the age of forty, and often at a much younger age. It is apt to be mistaken for Ewing's tumor of one of the long bones. It is strikingly radiosensitive and the prognosis is relatively favorable. The cells are large, with abundant cytoplasm which may show pseudopodia. The nuclear outline is indented or kidney-shaped. With a silver stain a delicate reticulum is seen to encircle single cells (Figs. 436 and 437, page 753).

**LIPOSARCOMA.**—This tumor arises from the marrow, but involves the bone. It is a soft, yellow, slowly-growing tumor, composed of large cells arranged in alveolar groups with abundant cytoplasm filled with fine droplets of fat. On this account the tumor may be confused with secondary hypernephroma.

**METASTATIC TUMORS.**—Secondary tumors of bone are most likely to occur in carcinoma of the breast, prostate, kidney (hypernephroma), and lung, but many other malignant tumors may be the starting-point of secondary deposits. (Fig. 523.) Cancer of the thyroid gland deserves special mention. The bones commonly affected are the ribs, vertebræ, sternum, skull, and the upper end of the femur and humerus. In all of these bones the marrow is of the red variety and is well vascularized. In the shaft of a long bone the metastasis is often at the site of the nutrient artery. From all this it is evident that the usual mode of infection is by the blood stream, and not by lymphatic permeation as used to be thought. The deposit is formed in the medullary cavity. Roentgen-ray evidence goes to show that most of the tumors are purely osteolytic, the destruction not being associated with any bone formation. A round well-defined lesion is seen similar to that of multiple myeloma, although not quite so punched-out in character. Hypernephroma affords a perfect example of an osteolytic process. Breast cancers are for the most part osteolytic, but a few are osteoblastic. Cancers of the prostate, on the other hand, are almost entirely osteoblastic, so that the lesions appear sclerotic in the roentgen-ray picture. A large amount of new bone is formed, which may obliterate the shaft and even form projections on the surface. Even here there is probably an associated osteolytic process, for fractures may occur. In the osteolytic form fractures are common, and may be the first sign of bone disease. It is rather remarkable that in spite of the destruction of bone, the fracture may heal satisfactorily. The blood picture may suggest a correct diagnosis. There is a leuco-erythroblastic anemia, with normoblasts and myeloblasts in the smear.

## THE OSTEODYSTROPHIES

There is a group of diseases of bone which is characterized by disorders of calcium metabolism and of ossification. Among these are osteitis fibrosa, osteitis deformans, osteomalacia, rickets, osteogenesis imperfecta, achondroplasia, hereditary chondrodysplasia, and marble bones. As they are disorders of the growth of bone they may be considered together under the heading of the osteodystrophies.

**Osteitis Fibrosa.**—This condition, also known as osteitis fibrosa cystica, may occur in a general or focal form. The two bear no relation to one another, although in both there may be the development of giant-cell tumors. The focal form is confined to young people, whilst the general



form may occur at any age. It is with the general form, sometimes called Von Recklinghausen's disease of bone, that we are concerned at present. It is very much rarer than the focal variety.

**CLINICAL FEATURES.**—The advanced clinical picture is easy to recognize, but the early stages may severely tax the diagnostic ability of the physician. The three principal symptoms are bone pains, tumor-like swellings and deformity of the bones, and spontaneous fractures. Of these, fracture is the most striking and often is the first sign of bone disease. The fracture heals more readily than might be expected from the rarefied condition of the bone, but this may be explained by the fact that bone formation is also active. Owing to the softening of the bones they may become markedly bowed, and in severe cases the most extreme deformities may develop. The bones most often affected are the humerus, femur, and tibia, in that order. The disease is progressive and fatal unless diagnosed and treated correctly. The roentgen-rays show widespread local rarefaction and sometimes cyst formation. The bones have a translucent and honeycombed appearance, the marrow is enlarged, and periosteum normal. The chemical changes in the blood, which are all-important, are described in the next section.

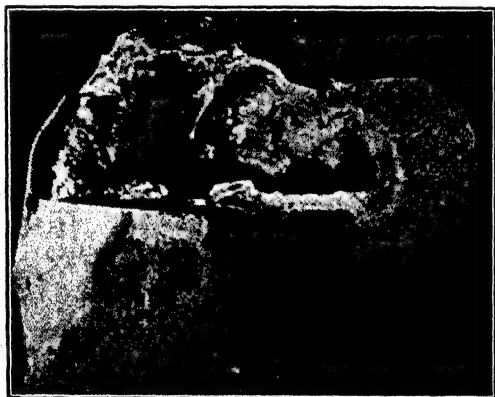


FIG. 524. —Osteitis fibrosa. The neck of the femur is converted into a large cystic cavity.

**LESIONS.**—In advanced cases the highly porous bones may be much deformed and curved; they may be so soft that they can be cut with a knife, and the compact bone may be greatly thinned by the formation of cysts. (Fig. 524.) These, however, are not necessarily present, so that osteitis fibrosa is a more correct name than osteitis fibrosa cystica. The cysts may contain watery fluid or gelatinous masses. Abundant callus is found at the site of a recent fracture. The *microscopic appearance* is supposed to be specific, but a similar histological picture may be met with in other diseases, as pointed out above. There is resorption of bone with marked osteoporosis. (Fig. 525.) This goes hand in hand with vigorous new formation of young fibrous tissue which occupies the dilated Haversian canals and takes the place of the absorbed bone. The marrow is also fibrosed. Some of this connective tissue may become converted into osteoid tissue, and formation of new bone can be detected with rows of osteoblasts,

lining the spaces in the bone, but resorption always outstrips ossification and osteoclasts and giant cells form easily recognizable clumps. The formation of multiple giant-cell tumors or osteoclastomata is a characteristic feature of the disease. These may be minute or they may form quite large tumors which can be detected clinically. The new connective tissue is poorly vascularized, so that degeneration, softening, and cyst formation may occur. The lesions are at first in the form of circumscribed patches and are most marked at the ends of the growing bones, but in time they may fuse. The patient may die of osteogenic sarcoma, but this tendency is not nearly so marked as in Paget's disease.

It was in 1901 that Von Recklinghausen gave the first accurate account of osteitis fibrosa, and in 1904 Askanazy reported a case associated with a parathyroid tumor, but a quarter of a century elapsed before the significance of this association was recognized. The bone lesions are a manifestation



FIG. 525.—Osteitis fibrosa, showing the marked osteoporosis and absorption of bone.  
× 50.

of hyperparathyroidism, due usually to an adenoma but occasionally to hyperplasia of the parathyroids. The biochemical changes are similar to those produced by the administration of parathyroid extract, and the osteoporosis and other bone changes can be reproduced experimentally in animals by continued administration of the extract. The calcium removed from the bones appears in the blood, and the blood calcium rises from 10 mg. per 100 cc. to 15 or 20 mg. The phosphorus is below normal (3 mg. per 100 cc.), because the renal threshold for phosphorus is lowered by excess parathyroid hormone. Normally the calcium and phosphate ions of the blood and calcium phosphate of the bones are in a state of equilibrium and are subject to the law of ionic dissociation, *i. e.*, concentration of the ions, if altered, must vary inversely with each other, so that excess of calcium ions causes fall of phosphate ions. If, however, renal insufficiency develops, as it is apt to do in the later stages of the disease, the

phosphorus may be retained and the level in the blood may return to normal. The low serum phosphorus is particularly valuable for differentiating hyperparathyroidism from such decalcifying diseases as widespread metastatic carcinoma of bone in which the blood may be flooded with calcium. Much valuable information regarding the chemical changes in the blood in this and other bone diseases will be found in Woodard's paper. In osteitis fibrosa the serum alkaline phosphatase is considerably raised, although less so than in Paget's disease. There may be metastatic calcification of the arteries, and deposition of calcium in the renal pelvis with calculus formation. Large quantities of calcium are excreted in the urine, so that there is a negative calcium balance. The results of removing the parathyroid tumor may be among the most dramatic of postoperative phenomena; the blood calcium falls below normal so that there may be danger of tetany, the bone pains may be abolished immediately, the giant-cell tumors may diminish in size in the course of a few weeks, the renal calculi may break into fragments which are passed into the bladder, there is a marked gain in weight, and cripples may throw away their crutches.

**FOCAL FORM OF OSTEITIS FIBROSA.**—This is very much commoner than the generalized form. It bears no relation to that condition, for it is unconnected with hyperparathyroidism and the blood calcium and plasma phosphatase are normal. It occurs at the end of one or more of the long bones during their period of growth and is often first discovered through a spontaneous fracture. Cyst formation is common, as is the formation of a giant-cell tumor. It is probably a perversion of the normal process of removal of calcified cartilage by vascular connective tissue preparatory to the formation of true bone. This matter has been discussed in connection with giant-cell tumor of bone.

**PAGET'S DISEASE.**—This condition, also known as *osteitis deformans* (although not nearly so deforming as Von Recklinghausen's disease), was first described by Sir James Paget in 1876. It is usually regarded as a rarity, but Schmorl, examining the entire skeleton in his autopsies, collected 138 cases in the course of five years. There is first softening and later overgrowth of bone; during the period of softening characteristic deformities develop. A number of bones are usually affected, but the disease may remain confined to one bone for many years. The former or polyostotic variety is common, but the latter or monostotic form is relatively rare, often remaining subclinical. The monostotic form is commonest in the tibia, the polyostotic is most frequent in the sacrum and vertebræ. It is not certain if they are variations of the same disease.

**Clinical Features.**—The disease usually begins over the age of forty. It may be familial. I know of two families in each of which three cases occurred. The legs are generally first affected, but the earliest change may be in the skull. The softened bones are bent, the femur outward, the tibia forward. They become hardened again in this position and look as if they had been bent by the hands of a giant. Persistent bone pains in the legs may appear before the deformity. The head enlarges, and the patient presents himself with a history that he has to buy hats of ever-increasing size. The head comes to present a very characteristic appearance, for it is a triangle with the base above, the face escaping almost completely. Occasionally the bones of the face are greatly thickened (*leontiasis ossea*). A kyphosis or

posterior curvature of the softened spine is very common and reduces the height of the patient. The general appearance in the advanced stage of Paget's disease is highly characteristic. The short squat figure with bent shoulders, curved back, sunken chest, and great head hanging forward, as it waddles along with bowed legs, out-turned toes, and the aid of a stick, is a living justification for the name *osteitis deformans*. The roentgen-ray picture is characteristic even before any deformity has appeared. The affected bones are thick and dense, although the medullary cavity is widened, and the vault of the skull presents a peculiar serrated (cock's comb) appearance which is pathognomonic. The disease is progressive, but, unlike *osteitis fibrosa*, does not usually shorten life. There is, however, a fairly strong tendency to the development of osteogenic sarcoma. When that tumor occurs over the age of fifty years it is almost always associated with Paget's disease. Arteriosclerosis is often very marked. The serum alkaline phosphatase is very high, and may be over 100 units.

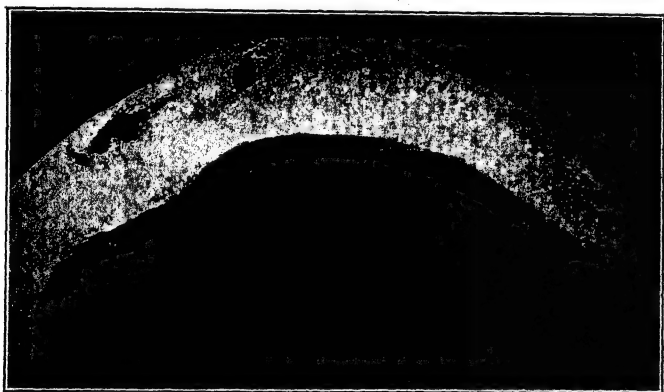


FIG. 526.—Paget's disease of the skull; great thickening of the bone and cyst formation.

**LESIONS.**—The bones commonly affected are the skull, vertebræ, and bones of the leg. In Schmorl's material the spine (including the sacrum) was most frequently involved. At first the bones are soft and easily cut with a knife; it is at this stage that the deformities occur. Later the bone becomes hard and of increased thickness. There is a thick deposit of subperiosteal bone on the long bones and on the skull, and the surface is rough and irregular. In spite of the thickening the new bone is of a porous character, as can be demonstrated by pouring water into the thick skull cap through which it runs as through a sieve. The thick, hard, curved bones are very characteristic of Paget's disease. The thickening is most strikingly seen on the cut surface of the skull cap, and a pathological diagnosis can readily be made from it alone. (Fig. 526.) *Microscopically* there is first a replacement of the original bone by connective tissue, and then a substitution of finely porous cancellous bone which gradually becomes harder. Absorption and apposition go on together, but the latter outstrips the former so that the bone becomes thick though still finely porous. One of the most characteristic features of the microscopic picture is the great number and *irregular* arrangement of the lamellar systems, which is seen in

no other disease of bone. This gives what is known as a *mosaic* structure (Fig. 527), due to variously shaped areas of new and old bone fitted together like pieces in a jig-saw puzzle. These pieces are not arranged around vascular canals to form Haversian systems; there is no formation of an "osteon." The cement lines are wide, prominent and irregularly scalloped. Cyst formation is very rare, and so is the formation of giant-cell tumors. The medullary cavity is filled with fibrous tissue. In about 10 per cent of cases sarcoma develops and kills the patient. This may be fibrosarcoma or osteogenic sarcoma. Fibrosarcoma, which is the commoner, arises from the new cellular connective tissue. The osteogenic sarcoma is not identical with the classic form, and may show great numbers of tumor giant cells.

There are often multiple foci of sarcoma in different bones.

The nature of the condition is uncertain. By some it is believed to be a variation of osteitis fibrosa occurring at a later age, but the blood calcium and phosphorus are normal, the alkaline phosphatase is higher, and there is no parathyroid hyperplasia. Edholm, Howard and McMichael have demonstrated that in generalized Paget's disease the bone blood flow is greatly increased, sometimes up to twenty times the normal. This produces the same effect on the general circulation as do free arteriovenous communications, with resulting congestive heart failure. This effect is not seen in the localized form. It is of interest to note that Paget considered the bones to be hyperemic, and in one of his original cases the heart was dilated at autopsy. Other guesses have been made, but they are too baseless to be mentioned.



FIG. 527.—Paget's disease of bone showing mosaic appearance.  $\times 200$ .

**OSTEOMALACIA.**—This is a very rare disease in North America, although fairly common in Europe and extremely so in China. It is considered in this place because for years it has been confused with osteitis fibrosa, but it is much more closely related to rickets. Osteitis fibrosa is an endocrine disorder; osteomalacia and rickets are deficiency diseases, the former affecting the adult, the latter the child. In all three the bones are poorly calcified, but in osteitis fibrosa the calcium is removed from the bones on account of parathyroid activity, while in osteomalacia and rickets calcium is not laid down in the bones because of lack of vitamin D, the other great regulator of calcium metabolism. Osteomalacia often comes on during pregnancy, owing to the great drain on the calcium of the woman's bones which occurs

at that period. Starvation may be a factor, and this probably accounts for the increase of the disease among the Central Powers during the war of 1914-1918. The disease is one of middle life, and is almost confined to women who are pregnant or exhausted by much childbearing. The bones commonly affected are the lumbar vertebrae, pelvis, and the bones of the legs. Osteomalacia provides a good example of the difficulty of drawing correct conclusions regarding the osteodystrophies. The parathyroids may be enlarged, but it is almost certain that the hyperplasia is secondary and not primary, an attempt to offset the deficient calcification of the bones. The same secondary parathyroid hyperplasia is seen in rickets.

As the name implies, the bones are softened owing to loss of calcium, so that they can be readily bent or cut. In the roentgen-ray picture they present a faint and lace-like appearance. The vertebrae are compressed, so that the patient becomes shorter. Owing to softening of the pelvis the promontory of the sacrum is pushed forward and the acetabula are pushed inward, so that the pelvic inlet is distorted and narrowed, making normal delivery impossible. The bones of the leg are markedly bowed. Microscopically the normal bone is replaced by newly-formed bone which is calcium-free, i.e., it remains as osteoid tissue. As Pick remarks, osteomalacia from the morphological standpoint is rickets in adult life, but the lesions are not most marked at the growing ends of the bone as in rickets, for growth of bone has now ceased.

**SENILE OSTEOPOROSIS.**—In the later period of life, particularly in women after the menopause, the bones tend to become rarefied. Bone absorption may be particularly marked in the vertebral column. The condition is due to a defect in the reparative mechanism of bone, the probable basis of which is the endocrine imbalance of later life, especially in the female (Albright). The notable feature of the blood chemistry is the lack of any abnormal findings. The absence of an elevation in the serum alkaline phosphatase serves to distinguish this condition from osteomalacia and from many metastatic tumors of bone (Woodard).

**OSTEOGENESIS IMPERFECTA.**—This rare condition, also known as *fragilitas ossium*, is an affection of childhood in which the bones are imperfectly ossified. There is marked hereditary and familial tendency. The child may be born dead with multiple fractures acquired *in utero*, it may be born alive and die afterwards from many fractures produced during delivery, or it may be born apparently healthy and only show evidence of brittleness during childhood and adolescence. There is a tendency for the condition gradually to disappear. A remarkable feature of the disease is that many of the patients have blue sclerotics; the color is due to partial visibility of the choroid through the sclerotic owing to some defect in that coat. Blue sclerotics may be associated with brittle bones in one member of the family, while the others have blue sclerotics but no special tendency to fractures. Otosclerosis may develop after the age of twenty years. The blood calcium and phosphorus are normal. The parathyroid glands may be enlarged. In one very severe case in a stillborn baby which I examined the enlargement was very noticeable. In addition to the fractures there may be bony swellings, especially in the temporal region so that the ears are turned out and down, and sometimes in the frontal or occipital regions. The ossification of the skull may be so incomplete that it is a mere membranous bag or a few bony plates; if ossification has proceeded further the skull may present a large number of Wormian bones. The teeth are poorly calcified and may be translucent. The bones are very light and fragile. Microscopically the trabeculae are narrow and widely separated. Few osteoblasts can be seen, and it is possible that there may be a deficiency of phosphatase production.

**MARFAN'S SYNDROME.**—In this remarkable condition there are anomalies of skeletal growth and of the mesenchymal tissue of the cardiovascular system. Marfan's original report in 1896 dealt with an extraordinary elongation of the distal

parts of the extremities in a five-year-old girl. Today the syndrome includes a tendency to great height, long and thin hands and feet, spinal curvatures, funnel or pigeon chest, dolicocephaly and bossing of the frontal bones, weakness of muscles, scanty subcutaneous fat, anomalies of the lens and other parts of the eye, defects of the cardiac septa, and medionecrosis of the aorta and pulmonary artery with a tendency to the formation of dissecting aneurism which is often fatal (Tung and Liebow). It is evident that in this disease, as in *osteogenesis imperfecta*, the defect of mesenchymal development is by no means confined to the skeleton.

**ACHONDROPLASIA.**—This is another rare defect in ossification, confined to bones ossified in cartilage, *i.e.*, long bones and base of skull; the rest of the skull and bones of the face develop normally. The child may die shortly after birth or may grow up as a stunted dwarf with short arms and legs, normal trunk, large head, depressed



FIG. 528.—Achondroplastic dwarf.

bridge of nose, and squat hands with fingers of equal length (trident hand). (Fig. 528.) The shortness of the bones is due to failure of the epiphyseal cartilage to function. The epiphyses are enlarged and with the short diaphysis give the bone the appearance of a collar stud. The indrawing of the nose is due to relative shortening of the base of the skull from imperfect ossification. Microscopically the cells of the epiphyseal cartilage are large, are not arranged in rows, and show an undisciplined tendency to grow in all directions; there is no evidence of active ossification. The disease, which is often familial, is probably due to some endocrine disorder. Dachshunds are achondroplastic dogs selectively bred.

**HEREDITARY CHONDRODYSPLASIA.**—This rare condition is also known as *multiple cartilaginous exostoses*. It appears to be a hereditary disturbance of the metabolism of cartilage and bone. It begins early in life and is commoner in boys than girls. Only the bones ossified in cartilage are affected, flat bones as well as long bones. The two chief changes are deformities from retardation of growth and multiple exostoses. The growth retardation may affect any bone developed in cartilage and sometimes only one part of a bone, *e.g.*, acromion process of scapula. The radius

or tibia may not grow properly while the ulna or fibula does, with resulting bowing of the bones. The radius becomes a bent bow; the ulna serves as its tight string. The exostoses appear on the shaft of the bones, often as the result of injury to the periosteum. At first they consist of cartilage, but later they may be completely ossified. There may be great numbers of these exostoses. Swellings may develop in the region of the epiphyseal lines, causing enlargement of the ends of the bones. The disease ceases when skeletal development is complete. Nothing is known as to the cause of the condition.

**MARBLE BONES.**—This extremely rare condition is also known as Albers-Schönberg's disease. A better name is *osteopetrosis*. The disease shows a strong familial tendency. It is characterized by excessive calcification of osteoid tissue and absence of true ossification as shown by lack of bone lamellæ and of osteoblasts. The bones therefore lose their elasticity and fractures are common. The condition occurs in childhood or can be traced back to that period. In the roentgen-ray pic-

ture the normal structure of bone is replaced by a homogeneous, intensely dense, marble-like appearance. The principal features may be catalogued as follows: All the bones are very dense, particularly the ends of the long bones; narrowing of the cranial foramina causes optic atrophy and other cranial nerve disturbances; narrowing of the medullary cavity leads to osteosclerotic anemia; hydrocephalus, interference with dentition, and enlargement of the liver and spleen may be present. The cause of the condition is unknown, but some suggestive work of Selye's may be noted. He found that when small doses of parathyroid extract (parathormone) are given to the experimental animal over long periods of time, instead of rarefaction there is apposition, *i.e.*, increased bone formation, owing to stimulation of the osteoblasts. The bones assumed the same extremely dense character as is seen in marble bones.

**HYPERTROPHIC PULMONARY OSTEO-ARTHROPATHY.**—This condition, also known as *Marie's disease*, is largely due to deficient oxygenation of the tissues, especially when associated with the absorption of toxins. It is met with, therefore, in such pulmonary conditions as bronchogenic carcinoma, bronchiectasis, chronic phthisis, empyema, and in congenital heart disease. A primary, idiopathic familial form may occur in which no focus of disease can be found elsewhere in the body. There is a subperiosteal formation of new bone with thickening of the bones of the hands and feet, and a lesser involvement of the long bones. The corresponding joints may show swelling and thickening of the synovial membrane. *Clubbing* of distal phalanges (fingers and toes) may be part of osteo-arthropathy or may occur apart from that condition, especially in subacute bacterial endocarditis. The clubbing is largely due to thickening of the soft tissues, probably from edema due to deficient oxygenation. The nails are thickened and characteristically curved, with or without an accompanying thickening of the phalanges.

**HYPEROSTOSIS FRONTALIS INTERNA.**—This obscure condition, also known as metabolic craniopathy, is characterized by a peculiar bossy thickening of the inner table of the frontal bone associated with metabolic and psychotic disturbances. The cranial capacity is decreased, with resulting atrophy of the frontal lobes. The radiological appearance is readily recognized. The metabolic changes are those of pituitary dysfunction, particularly obesity, virilism and menstrual disorders, and may precede the bony changes. In 99 per cent of the cases the patients are women, usually after the menopause. There may be no metabolic or psychotic symptoms, and the bony lesions may be discovered by chance at autopsy. The etiology is unknown.

**Fibrous Dysplasia of Bone.**—Attention has been drawn by Lichtenstein and Jaffe to a condition which may readily be confused with osteitis fibrosa cystica. It appears to be a congenital anomaly in development resulting in tumor-like malformation of bone, and has been appropriately named fibrous dysplasia. One or several bones may be involved. Of 134 cases reviewed by Pritchard only 28 were monostotic. Where the condition is multiple the lesions tend to be unilateral. The most common site is the upper end of the femur, which is often bowed outward. Fibrous dysplasia appears most commonly in early life, and the greatest activity is during the growth period. Many cases are asymptomatic, but pathological fracture may occur. Almost any bone may be involved. I have seen one case in which two adjoining ribs presented huge swellings mistaken for giant-cell tumor, and another in which there was cyst formation in the skull. In the severe forms, usually occurring in childhood, there may be extra-skeletal anomalies such as pigmentation of the skin, premature sex develop-



ment in females, premature growth, and hyperthyroidism. These are known collectively as *Albright's syndrome*.

The affected part of the bone is expanded and the cortex is thinned, the interior being filled with rubbery, sometimes gritty, fibrous connective tissue. The microscopic appearance of the connective tissue varies; in some places it may be cellular, with spindly cells arranged loosely in whorls (Fig. 529) whilst elsewhere it may be densely collagenous. New trabeculae of bone may be formed through metaplasia of the connective tissue, thus accounting for the grittiness referred to above. In addition there may be small cysts, occasional hemorrhage, and giant cells. In the x-ray film there is a localized rarefaction which is readily mistaken for cyst formation.



FIG. 529.—Fibrous dysplasia of bone.  $\times 160$ .

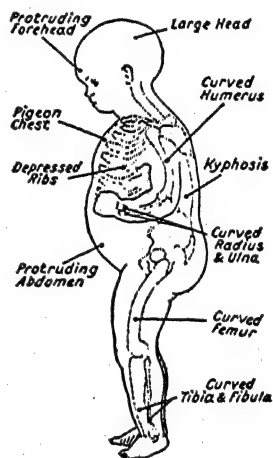


FIG. 530.—Clinical features of severe rickets. (Harris, *Vitamins in Theory and Practice*, courtesy of Cambridge University Press.)

**Rickets.**—Rickets is a deficiency disease in which an osteodystrophy is responsible for some of the main clinical symptoms, but its effects are by no means confined to the skeleton. It is a fascinating disease to study because of the remarkable advances in knowledge which have been made owing to the combined efforts of the biochemist, the experimental pathologist, the radiologist, and the clinician.

**ETIOLOGY.**—Rickets is a deficiency disease in which the inorganic constituents of bone, calcium and phosphorus are not properly utilized. Deficiency of four factors has to be considered: calcium, phosphorus, vitamin D, and light. Phosphorus deficiency is more serious than calcium deficiency. Vitamin D facilitates the absorption of calcium and phosphate from the intestine. Light, or rather the short wave ultra-violet rays, activates the sterols in the skin and converts them into vitamin D.

These four deficiency factors must be considered collectively, for they often act together. Thus an amount of calcium in the diet sufficient to prevent rickets becomes insufficient when the phosphorus is also lowered, even though only to a moderate degree. The two seem to work hand in hand. The same is true of the action of light. When rats are fed on a rickets-producing diet they can be protected by being rayed for two minutes each day with the mercury-vapor-quartz lamp. In actual practice rickets is a disease of the slums of large cities especially in countries which get little sunshine. Here all four factors are at work: the food is deficient in quality as well as quantity (calcium, phosphorus, and vitamin D) and there is a deficiency of ultra-violet light. The fault lies in the quality rather than the quantity of the food. A child may be starved and emaciated, yet show no sign of rickets, while a plump baby may be markedly rachitic. A diet almost exclusively of carbohydrates or proteins will produce rickets, but the addition of cod-liver oil will cure the disease. If the child gets a proper diet and sufficient sunlight, cod-liver oil is never necessary. Rickets is a disease of bottle-fed babies, except in the case of negro children whose dark skin prevents the light from activating the ergosterol.

**CLINICAL FEATURES.**—Rickets is a disease of infancy and early childhood covering the period from six months to two years, but the bony changes then instituted may persist for the rest of the patient's life. It is a disorder of calcium and phosphorus metabolism, and examination of the blood shows that either there is a low serum calcium with a rather low inorganic phosphate or normal calcium with very low phosphate. Among the constitutional symptoms are anemia, enlargement of the spleen and lymphoid tissue, flabbiness of the muscles, sweating, and poor formation of the teeth. The bony changes are the combined result of defective calcification and excessive proliferation of epiphyseal cartilage (Fig. 530). The bones are soft, so that the femur bends outward, the tibia forward, and the spine backward (kyphosis) or laterally (scoliosis). The constant pull of the tendo Achilles on the foot in the sitting position may produce a curved sabre-shaped tibia. In the softened pelvis the promontory of the sacrum is pushed forward and the acetabula inward, giving the same narrowed pelvic inlet as is seen in osteomalacia and constituting an insuperable obstacle to normal delivery in later life. The sternum is pushed forward (pigeon breast), leaving a vertical groove on each side of the thorax. The epiphyseal proliferation gives rise to a series of nodules at the costo-chondral junctions (the rickety rosary), and to nodular swellings at the wrists, knees, and ankles. Bones developed in membrane also suffer, and there is heaping up of spongy bone (bossing) in the frontal and parietal regions so that the skull becomes box-like. There may be a thinning of the back of the skull where the head rests on the pillow, a condition known as craniotabes. This is due to absorption of the non-calcified osteoid tissue from pressure. In the roentgen-ray picture the normal thin epiphyseal line is broad and irregular; periodic examination of this line forms a convenient method of estimating the effects of treatment, and has been much used in experimental work.

**LESIONS.**—The essential rachitic lesion is an abundant formation of osteoid tissue which fails to become calcified. The bones are therefore soft and the epiphyses can be cut with a knife. The degree of involvement of the ends of the long bones is proportionate to the rapidity of growth of the epiphyseal cartilage. The most rapid growth occurs at the junction of the ribs and costal cartilages, the lower end of the femur, and the upper end of

the humerus in that order. The widening of the epiphyseal line can be seen with the naked eye; it may be 10 or 15 mm. in diameter and is markedly irregular. It is widened not only in depth but also laterally, thus accounting for the nodular swellings of the ribs and at the ends of the long bones.

The *microscopic picture* is one of osteoid tissue formation without calcification. The cartilage cells are not arranged in rows as in normal growing bone, and the zone of proliferating cartilage may be ten times as deep as normal, sending out prolongations into the metaphysis which give the line the irregularity so characteristic of the gross appearance. (Fig. 531.) The zone of preparatory calcification is almost completely free of calcium. Beyond this there is a broad zone of osteoid tissue containing trabeculae and resembling bone morphologically, but without the all-important lime salts. The osteoid tissue extends out to the perichondrium, where it causes



FIG. 531.—Rickets. There is extreme widening of the epiphyseal line and thickening of the bone in this region. There is complete absence of calcification of the osteoid tissue.  $\times 7$ .

the characteristic thickenings observed clinically. The bosses on the skull and the new periosteal and endosteal bone are also composed of this same material. When healing occurs there is active calcification of the osteoid tissue so that dense bone is formed. In course of time much of this new bone (rickety rosary, etc.) disappears.

**Scurvy-rickets.**—This condition, also known as *infantile scurvy* and *Barlow's disease*, is a form of scurvy and bears no relation to rickets. It is characterized by subperiosteal hemorrhages, and is considered in connection with vitamin C deficiency in Chapter 11.

**RENAL RICKETS.**—This condition has already been described in Chapter 24. In children suffering from chronic renal insufficiency the bones may develop lesions similar to those of rickets. Osteoid tissue is formed in excess but not calcified, so that deformities occur. The relationship between the bone and renal lesions is not at present understood, but the disturbance of growth is supposed to be connected with the marked retention of phosphorus which constitutes the most striking of the bio-

chemical changes. As the concentration of ions varies inversely, the calcium falls as the phosphate rises, and this leads to drainage of calcium from the bones. In some cases it is possible that the primary defect may be in the parathyroids, the changes in the kidneys being secondary.

**CELIAC RICKETS.**—In celiac disease, characterized by the passage of voluminous fatty stools in young children, there is frequently marked osteoporosis with a tendency to spontaneous fracture, and occasionally there is typical evidence of rickets at the epiphyses. In this case the etiological factor is faulty absorption of calcium in the intestine.

**BONE CHANGES IN GAUCHER'S DISEASE.**—In Gaucher's disease, the bones may occasionally show marked changes (Pick). The marrow cavity is infiltrated with large lipid-filled Gaucher cells. Owing to a similar infiltration the cortex may appear to be coarsely vacuolated or may be greatly thinned, so that spontaneous fractures occur. The vertebrae suffer severely; their bodies may be crushed, with resulting shortening of the body length and the production of spinal deformities. In the roentgen-ray picture, in addition to general decalcification, there are large defects in the bone and thinning of the cortex.

## ADDITIONAL READING

- Absorption of Bone.** JAFFE: Arch. Surg., 1930, 20, 355.  
**Achondroplasia.** OPIE AND ALLISON: J. Med. Res., 1917, 36, 277.  
**Bence-Jones Protein.** MEYLER: Arch. Int. Med., 1936, 57, 708.  
**Chondrosarcoma of Bone.** LICHTENSTEIN AND JAFFE: Am. J. Path., 1943, 19, 553.  
**Eosinophilic Granuloma.** BASS: Am. J. Dis. Child., 1941, 61, 1254. FARBER: Am. J. Path., 1941, 17, 625. JAFFE AND LICHTENSTEIN: Arch. Path., 1944, 37, 99. LICHTENSTEIN AND JAFFE: Am. J. Path., 1940, 16, 595. OTANI AND EHRlich: Am. J. Path., 1940, 16, 479.  
**Ewing's Tumor.** COPELAND AND GESCHICKTER: Arch. Surg., 1930, 20, 246, 421. GESCHICKTER AND MASERITZ: J. Bone and Joint Surg., 1939, 21, 26. LICHTENSTEIN AND JAFFE: Am. J. Path., 1947, 23, 43. WILLIS: Am. J. Path., 1940, 16, 317.  
**Fibrous Dysplasia of Bone.** ALBRIGHT, *et al.*: New England J. Med., 1937, 216, 727. LICHTENSTEIN: Arch. Surg., 1938, 36, 874. LICHTENSTEIN AND JAFFE: Arch. Path., 1942, 33, 777. PRITCHARD: Am. J. Med. Sci., 1951, 222, 313.  
**Giant-cell Tumor.** AEGERTER: Am. J. Path., 1947, 23, 283. GESCHICKTER AND COPELAND: Arch. Surg., 1929, 19, 169. JAFFE, *et al.*: Arch. Path., 1940, 30, 993.  
**Hyperostosis Frontalis Interna.** KNIES AND LEFEVER: Ann. Int. Med., 1941, 14, 1858.  
**Liposarcoma of Bone.** FENDER: Am. J. Path., 1933, 9, 909. STEWART: Am. J. Path., 1931, 7, 87.  
**Marble Bones.** McCUNE AND BRADLEY: Am. J. Dis. Child., 1934, 48, 949. PIRIE: Am. J. Roentgenol., 1933, 30, 618. ZAWISCH: Arch. Path., 1947, 43, 55.  
**Marian's Syndrome.** TUNG AND LIEBOW: Laboratory Investigation, 1952, 3, 382.  
**Metabolic Bone Disease.** ALBRIGHT AND REIFENSTEIN: The Parathyroid Glands and Metabolic Bone Disease, Baltimore, 1948.  
**Multiple Myeloma.** DAHLIN AND DOCKERTY: Am. J. Path., 1950, 26, 581. GESCHICKTER AND COPELAND: Arch. Surg., 1928, 16, 807. JACKSON, *et al.*: Am. J. Med. Sci., 1931, 181, 169. LICHTENSTEIN AND JAFFE: Arch. Path., 1947, 44, 207.  
**Osteitis Fibrosa.** HUNTER: Quart. J. Med., 1931, 24, 393; Brit. J. Surg., 1931, 19, 203. JAFFE: Arch. Path., 1933, 16, 63. SCHMORL: Verhandl. d. deutsch. path. Gesellschaft, 1926, 21, 71. WOODARD: Arch. Surg., 1943, 47, 368.  
**Osteodystrophies.** PICK: Harvey Lectures, 1931-1932, p. 179.  
**Osteogenesis Imperfecta.** WEBER: Arch. Path., 1930, 9, 984.  
**Osteogenic Sarcoma.** COLEY AND POOL: Ann. Surg., 1940, 112, 1114.  
**Osteoid Osteoma.** JAFFE AND LICHTENSTEIN: J. Bone and Joint Surg., 1940, 22, 645. SHERMAN: J. Bone and Joint Surg., 1947, 29, 918.  
**Osteoporosis.** HOWARD: Canad. Med. A. J., 1950, 63, 258.  
**Page's Disease.** EDHOLM, *et al.*: Clin. Science, 1945, 5, 249. JAFFE: Arch. Path., 1933, 15, 83. SCHMORL: Virchows Arch. f. path. Anat., 1932, 283, 694.

- Plasmacytoma, Solitary.** STEWART AND TAYLOR: *J. Path. and Bact.*, 1932, **35**, 541.
- Renal Rickets.** HUNT: *Am. J. Dis. Child.*, 1927, **34**, 234.
- Repair of Bone:** GALLIE AND ROBERTSON: *Brit. J. Surg.*, 1919, **7**, 211. HAM: *J. Bone and Joint Surg.*, 1930, **12**, 827; *Cartilage and Bone*, in Cowdry's *Special Cytology*, New York, 1932. NIVEN: *J. Path. and Bact.*, 1931, **34**, 307.
- Reticulum-cell Sarcoma.** PARKER AND JACKSON: *Surg., Gynec. and Obst.*, 1939, **68**, 45.
- Rickets.** HESS: *Rickets, Including Osteomalacia and Tetany*, Philadelphia, 1929. SCHMIDT: in Henke-Lubarsch: *Handb. d. spez. path. Anat.*, Vol. 9, pt. 1, Berlin, 1929.
- Sarcoma and Radio-activity.** MARTLAND: *Am. J. Cancer*, 1931, **15**, 2435.
- Secondary Tumors.** JOLL: *Brit. J. Surg.*, 1923, **11**, 38.
- Senile Osteoporosis.** ALBRIGHT, *et al.*: *Trans. Assn. Am. Physicians*, 1940, **55**, 298; *J. A. M. A.*, 1941, **116**, 2465. WOODARD: *Arch. Surg.*, 1943, **47**, 368.
- Tumors.** CHRISTENSEN: *Ann. Surg.*, 1925, **81**, 1074. EWING: *Arch. Surg.*, 1922, **4**, 485. GESCHICKTER AND COPELAND: *Tumors of Bone*, New York, 1936.

## Chapter

# 33

## THE JOINTS

**DESCRIPTIVE OUTLINE.**—In describing disease in a joint the following structures should be considered: synovial membrane, contents of synovial cavity, articular cartilage and underlying bone, joint capsule and ligaments, periarticular tissues, overlying skin. The synovial membrane is thin, but it may be greatly thickened in disease. Its surface and that of the articular cartilage is smooth and glistening. The synovial cavity, which is merely a potential one, contains only a few drops or rather a film of fluid.

### ACUTE ARTHRITIS

Acute inflammation of a joint is caused either by bacterial infection or by trauma, such as a blow or sprain. *Trauma* gives rise to a mild though acute inflammation. The joint is swollen, the swelling being due partly to an increase of synovial fluid which may become cloudy or blood-stained, partly to inflammatory swelling of the synovial membrane which is congested and infiltrated with leucocytes. The *bacterial infections* may be suppurative or non-suppurative.

**Suppurative Arthritis.**—The common infecting organisms are staphylococci and streptococci. The suppuration may be part of a pyemia in septicemic conditions such as ulcerative endocarditis or puerperal sepsis, or no other focus may be found. The infection may spread from the bone as in acute osteomyelitis, or may be introduced from without by a perforating wound of the joint. In pyogenic infections such as pneumonia and meningococcal meningitis there may be suppuration of one or more joints.

In suppurative arthritis the *synovial membrane* is hyperemic, swollen, soft, and infiltrated with pus cells. The cells lining the surface are cast off, and fibrin is deposited on the raw surface. The *synovial fluid* is milky or frankly purulent, crowded with polymorphonuclear leucocytes, and usually contains the infecting organisms. The *articular cartilage* becomes eroded and the underlying bone is exposed, causing great pain when the joint is moved. The *ligaments* are softened and give way, so that the joint becomes completely disorganized and is often dislocated. The *capsule* may then rupture, the pus making its way into the periarticular tissues. This is a picture of the most severe form of suppurative arthritis. In other cases the infection is milder and may be localized to the synovial membrane (*acute synovitis*), with little or no destruction of the joint. When there has been destruction of tissue there will be fibrous union (ankylosis), and if the articular surfaces are destroyed the union may be cartilaginous or bony.

**Non-suppurative Arthritis.**—Most examples of acute arthritis are non-suppurative, the inflammation is confined to the synovial membrane

(acute synovitis), there is no destruction of tissue and therefore no permanent stiffness. *Traumatic synovitis* due to a strain is a good example of the condition. The synovial membrane is swollen, juicy, and congested, and infiltrated with inflammatory cells, while the synovial fluid is increased in amount, cloudy, and contains desquamated endothelium and small numbers of leucocytes. *Rheumatic arthritis* is the acute non-suppurative arthritis of rheumatic fever. Several joints are affected one after the other. There is an acute synovitis with excess of turbid fluid in the joint. Extreme tenderness is characteristic of the swollen and acutely inflamed joint. There is some involvement of the subsynovial and periarticular tissue and ligaments, and rheumatic nodules similar in structure to the Aschoff bodies in the heart may be present in the subcutaneous tissues. The inflammation usually undergoes complete resolution, but if there is severe involvement of the periarticular tissue, some permanent stiffness may result. The possible relationship of acute rheumatic arthritis to rheumatoid arthritis is discussed in the next section.

### CHRONIC ARTHRITIS

The term chronic arthritis has come to be used in a special sense. It does not mean, as the name suggests, a chronic inflammation of the joint, but a slow, progressive, crippling disease. It is not generally realized that this is the greatest single cause of prolonged disability in the world today. Thus in Sweden 9 per cent of all cases of permanent pensionable invalidity are due to arthritis, while in the state of Massachusetts the cases of disability number 140,000, compared with 25,000 from tuberculosis. The Metropolitan Life Insurance Company of New York estimates that the disease is responsible for an annual loss of 7,500,000 weeks of work and costs \$200,000,000. The English figures are very similar. The groups are rheumatoid arthritis and osteoarthritis, which are sometimes included under the common heading of arthritis deformans, a name only too well justified. Rheumatoid arthritis has also been called chronic infective, degenerative and proliferative arthritis, the last name indicating the proliferation of synovial membrane which is the dominant characteristic. Osteoarthritis is also called hypertrophic arthritis because of the overgrowth of perichondral tissue resulting in "lipping" of cartilage and bone around the joint. It must be noted, however, that synovial membrane and cartilage are relatively simple structures which may respond to stimuli either by proliferation or degeneration, and that the same end result may be produced by a variety of agents, and the same agent may produce a variety of gross appearances (Sherman). Foci of round cell infiltration in the synovial membrane do not necessarily spell infection, and the most intense inflammation may be present as the result of non-infective lesions. All of which indicates how difficult it is to reach conclusions regarding the etiology of chronic arthritis.

**Rheumatoid Arthritis.**—This form commonly occurs in women of between twenty and forty years, *i. e.*, during the period of reproductive activity. The onset is gradual and insidious, but in children it may be quite acute, with multiple arthritis, fever, leucocytosis and enlargement of the spleen

and lymph nodes, a condition known as *Still's disease*. A practically identical condition in adults, except that there is leucopenia in place of leucocytosis, is somewhat unjustifiably dignified by the name of *Felty's syndrome*. In rheumatoid arthritis the small joints of the hands and feet are the chief sufferers, but the larger joints may be involved later, the hip usually escaping. The course of the disease is marked by remissions and exacerbations, and at any time it may be arrested, but the injury to the joint is permanent, and the hands and feet are twisted, gnarled, and crippled for life. About 20 per cent recover completely, 60 per cent are left with minor disabilities, and 20 per cent remain severely disabled. The



FIG. 532.—Subcutaneous nodules in rheumatoid arthritis. (Kindness of Dr. A. J. Blanchard.)



FIG. 533.—Synovial fringes in chronic arthritis.

affected joints show a doughy spindle-shaped swelling, and the overlying skin may be tight and glossy. Ulnar deviation of the hand is a characteristic deformity. In from 15 to 20 per cent of the cases careful search will reveal the presence of painless subcutaneous nodules similar to those which are so characteristic of rheumatic fever. The usual site is the dorsal surface of the forearm a short distance below the olecranon. (Fig. 532.) They vary in size from seed-like bodies to nodules as large as an olive. They may persist for months and years and then disappear. The subcutaneous nodule is not found in osteoarthritis. There are often general signs of chronic infection such as malaise, occasional fever, anemia, palpitation, sweating, increased sedimentation rate and a general toxic appearance.



The spleen and lymph and lymph nodes may be enlarged, especially in children.

**ETIOLOGY.**—An enormous amount has been written about the causation of rheumatoid arthritis, a sure indication that little is known about the subject. But a few generalizations are justified. The condition belongs to the group of the collagen diseases, the essence of which is a loosening and degeneration of the ground substance of connective tissue. Arthritis of similar type occurs in disseminated lupus and generalized scleroderma, and old or active lesions of rheumatic heart disease are present in over half the cases (Baggenstoss and Rosenberg). Rheumatoid arthritis probably represents an allergic reaction to a bacterial antigen. Clinical signs of infection, such as those enumerated above, are the rule. A history of recurring infections in the naso-pharynx, genito-urinary tract, etc., can often be obtained. It should be realized, however, that there is no real proof that rheumatoid arthritis is related to infection, and the allergy may not be to bacteria. The theory that dental infection was the cause of the condition perhaps originated with the King of Assyria who was told by his physician 2500 years ago that the pains in his head and limbs were due to his teeth and that he should have them extracted. This plausible theory finally reached the status of an accepted fact, with the consequent loss of countless numbers of teeth. The matter is discussed more fully in connection with the subject of focal infection in the chapter on Dental Pathology. The target tissues, in this case the joints and subcutaneous connective tissue, may be conditioned by such factors as the steroid hormones. It was the remarkable remissions produced by pregnancy and obstructive jaundice that pointed the way to the adrenal cortex and the discovery of cortisone, a hormone which not only produces a dramatic improvement in the clinical picture, but an equally remarkable change in the lesions both in the joints and the skin nodules.

**LESIONS.**—The synovial membrane is primarily affected, so that the disease might be called synovioarthritis in contrast to osteoarthritis. If the joint is opened in the operating room the *synovial membrane* is seen to be congested, edematous, redundant, and swollen so as to form pulpy masses or fringes and tags. (Fig. 533.) Microscopically it consists of vascular granulation tissue infiltrated with leucocytes and mononuclear cells of various kinds, with sometimes great numbers of plasma cells. (Fig. 534.) The surface may be covered by a thin layer of necrotic material containing leucocytes. The *synovial fluid* is increased in amount and may be cloudy in character owing to the large number of the cells which it often contains. The mucin of the synovial fluid is similar to the mucin of the intercellular ground substance, consisting of hyaluronic acid bound to protein, and is probably produced by the numerous mast cells of the synovial membrane (Asboe-Hansen). The mast cells are known to be the source of heparin, which is closely related to hyaluronic acid. The cells which float in the fluid are degranulated mast cells. In rheumatoid arthritis the viscosity of the fluid is reduced owing to depolymerization of the hyaluronic acid.

The disease may be arrested at this stage, remaining a mere synovitis. Usually, however, the *articular cartilage* is involved. It is attacked both

from above and below. The synovial membrane grows over it from the side, forming a thick vascular covering or *pannus* which becomes adherent to the cartilage and eats it away. The idea that pannus creeps over the surface of the articular cartilage and burrows under it may be quite wrong. It is possible that the destruction of the cartilage is due to dedifferentiation of the cartilage with accompanying disintegration in a similar fashion to the changes seen in the other collagen diseases (Collins). The cartilage is also attacked from below by granulation tissue which is formed in the superficial layers of the epiphysis as part of the inflammatory reaction. As a result of this combined attack the cartilage is destroyed. Adhesions are formed between the two layers of pannus covering the articular surfaces, and the joint cavity may be obliterated. Fibrous ankylosis of the joint develops and in time the ankylosis may become bony. The *periarticular*

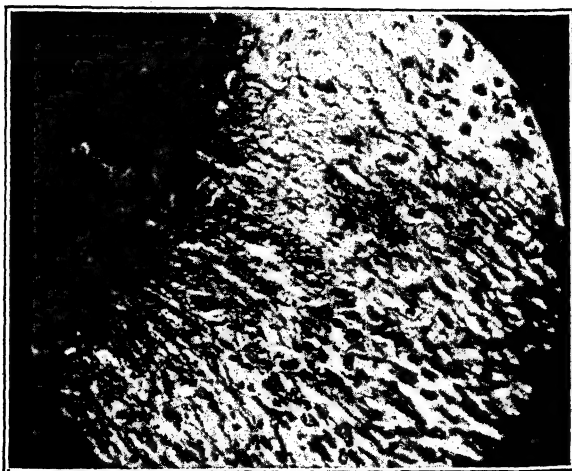


FIG. 534. —Rheumatoid arthritis.

*tissue* shares in the inflammatory swelling and edema. The *muscles* of the part undergo marked atrophy; the extensors of the fingers are especially affected, so that the swollen fingers show a characteristic flexion. It has been shown by Steiner and his associates that this atrophy is the result of an inflammatory nodular polymyositis involving widely separated muscles. When first described these muscle lesions were thought to be specific for rheumatoid arthritis, but Ogryzlo has found identical lesions in a wide variety of conditions, so that they must be regarded as non-specific. The *subcutaneous nodules* bear a striking resemblance to the similar nodules found in rheumatic fever, and provide the best picture of the microscopic lesion of rheumatoid arthritis. There is a large area of central necrosis surrounded by a zone of large mononuclear cells arranged in radial fashion. The arterioles in the surrounding tissue often show obliterating endarteritis and deposits of fibrin under the endothelium. The perineurium

of the peripheral nerves may show multiple inflammatory lesions similar in type to the subcutaneous nodules (Freund *et al.*). Changes in the pituitary have been described which may be significant. The mucoid cells (basophils and some chromophobes) are those which contain mucoprotein granules that stain with the periodic acid-Schiff method. In rheumatoid arthritis these cells undergo a degeneration comparable to the change (Crooke-Russell cells) seen in Addison's disease (Pearse).

**Osteoarthritis.**—In its typical form this degenerative joint disease differs from rheumatoid arthritis in almost every respect. It is commoner in men than in women, especially the form which affects the hip joint; it is a disease of the later period of life; there are no general symptoms; there is no evidence of a toxic factor; the large joints are commonly involved, often only one joint; there is no true ankylosis. The hip joint (*morbis coxae senilis*) offers an excellent example of the monoarticular form occurring in elderly men. The small joints of the hands and feet may also be involved, and it is in them that the clinical manifestations can be more readily studied. The knuckles become greatly swollen and knobby. *Heberden's nodes*, which are much commoner in women, are often present; these are small bony outgrowths at the sides of the terminal phalangeal joints. In the early stage the node is a soft nodule containing a bead of mucoid material, and arises as the result of degeneration of the periarticular soft tissue with subsequent ossification. Movement may be much limited by osteophytic outgrowths, but there is no ankylosis.

**ETIOLOGY.**—The cause of the degeneration is unknown. It is a slow involutional process often associated with marked arteriosclerosis, so that local ischemia may play a part. It is always difficult to form a correct judgment of the relation of trauma to any pathological process, but the common idea that trauma is an etiological factor, especially in hip joint disease, appears reasonable. If a joint is continually exposed to trauma, as in professional athletes (*e. g.*, baseball catcher) or in the course of a trade, it may show the characteristic changes. Degenerative arthritis appears to be a process associated with the ageing of the tissues of the joints. It may be described as "wear and tear" arthritis. Similar changes are found in the knee joint in routine autopsies with increasing frequency with advancing age (Keefer, Parker). The primary lesion appears to be a loss of chondroitin sulphate from the ground substance of the articular cartilage. The collagen fibrils are left unsupported, so that they are vulnerable to the mechanical effects of trauma and wear and tear. Erosion of cartilage in these knee joints is commonest over areas of contact subjected to the greatest movement, strain, weight bearing, and injury. As a result of gradual loss of elasticity in the articular cartilage the subchondral bone is no longer protected from the irregular localized effects of weight and pressure, and the changes characteristic of degenerative arthritis result. Age may therefore act in two ways: by reducing the elasticity and by representing trauma spread over a period of years. Similar lesions are present in horses and mules (Callender and Kelser). Loss of cartilage is the primary lesion, followed by bone production which is secondary but has given the name of hypertrophic arthritis to the disease.

	RHEUMATOID ARTHRITIS	OSTEOARTHRITIS
SEX:	Common in female.	Common in male.
AGE:	Generally under forty years.	Generally over forty years.
ONSET:	Gradual but sometimes acute.	Always gradual.
JOINT LESIONS:	An inflammatory condition of synovial membrane. Early lesions in metacarpo - phalangeal joints and wrists; symmetrical and migratory.	A degenerative condition of cartilage and bone. Early lesions in terminal interphalangeal joints, hips, and knees; often unilateral and fixed.
GENERAL SYMPTOMS:	Toxic symptoms, fever, loss of weight, anemia, low basal metabolic rate.	No constitutional disturbances.
LOCAL SIGNS:	Local signs of inflammation, marked deformity, extreme atrophy of muscles, swelling of soft parts, subcutaneous nodules, fibrous or bony ankylosis. Marked pain. Complete crippling in 10 per cent.	No local inflammation, deformity not marked, muscular atrophy only from disuse, soft parts not swollen, Heberden's nodes and no true ankylosis. Little or no pain. Complete crippling rare.

**LESIONS.**—Osteoarthritis is a degeneration of articular cartilage and bone; in this it differs from rheumatoid arthritis which is primarily an inflammation of synovial membrane. The *cartilage*, both its cells and matrix, degenerate, and the smooth surface becomes roughened. The cartilage cells swell, burst, and disappear, and the matrix undergoes a perpendicular fibrillation which accounts for the velvety surface. The softened cartilage is gradually worn away until the underlying bone is exposed. In a hinge joint (elbow, knee) the process of attrition is irregular, so that parallel furrows and ridges are formed. The periphery of the cartilage has a much better blood supply than the central part and survives the general downfall. The *bone* degenerates together with the cartilage, but the exposed surface undergoes a curious process of condensation and hardening, as a result of which it becomes polished like ivory. This appearance is known as *eburnation* (*eburneus*, ivory), and no really satisfactory explanation of the process can be given at present. Deep to the condensed layer the bone is degenerated, rarefied, and becomes absorbed, so that the greater part of the head and neck of the femur may disappear. In addition to central atrophy there is peripheral proliferation. Cartilaginous excrescences are formed at the margin of the articular cartilage which resemble candle drippings and cause lipping of the edge of the joint. They increase the available articular surface and may be compensatory in character. They tend to become ossified and osteophytes are also formed farther out, so that the atrophied head of the bone is surrounded by a ring of excrescences which greatly limit movement.

It is because of these changes, which form a striking feature in the roentgen-ray picture, that this variety is sometimes called by the misleading name of the hypertrophic form of chronic arthritis. In osteoarthritis of the spine osteophytes may press on the nerve roots as they emerge from the foramina, giving rise to referred pains. Thinning of the intervertebral discs is a feature of diagnostic importance in the x-ray film, as it does not occur in ankylosing spondylitis. The *synovial membrane* may become fibrous and fatty, and sometimes presents shaggy fringes which may be changed into cartilage and become detached to form the foreign bodies known as *joint mice*. The *ligaments* share in the general degeneration and dissolution, so that dislocation may occur finally.

**Ankylosing Spondylitis (Marie-Strümpell).**—The chronic disabling disease of the spine, first described by Pierre Marie in 1898 and known as Marie-Strümpell spondylitis, may be more related to rheumatoid arthritis than to osteoarthritis. It is, however, very much commoner in males (15 to 1), usually beginning before the age of thirty. The etiology is uncertain, but certain features point to a chronic infection, *viz.*, low grade fever, tachycardia, high sedimentation rate, weight loss and wasting of muscles. Romanus suggests that the lesions are the result of infection starting in the prostate and seminal vesicles and extending by the vertebral system of veins and lymphatics first to the sacro-iliac joints and later to the spine.

The essential *lesions* occur in the joints of the vertebral column. There is a synovitis, with increased vascularity, proliferative changes in the synovia, and infiltration of the tissues with lymphocytes and plasma cells. Later the articular cartilage is destroyed, fibrous adhesions are formed, and there is eventual bony fusion. Some of the earliest and most characteristic changes occur in the sacro-iliac joints, which may be demonstrated long before the onset of symptoms in the back. There is destruction and narrowing of the joint space, which appears in roentgen films as a fuzziness of the opposed surfaces of the bones. Later in the disease there is calcification followed by ossification of the various vertebral ligaments including the anterior spinal ligament and finally the intervertebral discs with bony ankylosis. The condition now is well described by the term "poker back." The rigidity is extreme, the normal spinal curvatures are lost, and the cervical spine is curved into a bow which forces the miserable man's head down until his chin touches his chest. The state of the patient when these changes are complete can be better pictured than described.

Although the progress of the disease may be as relentless as described, the process may be arrested at any stage. Involvement of the large peripheral joints (hip, knee, shoulder, etc.) occurs in 15 to 25 per cent of cases, the lesions closely resembling those of rheumatoid arthritis. Whether the disease is merely a special expression of rheumatoid arthritis or is a separate pathological entity remains a matter of dispute. Whilst the condition resembles rheumatoid arthritis in many respects, the calcification of ligaments, predominance in males, lack of response to gold therapy and infrequency of streptococcal agglutinins in the blood are quite distinct from that disease.

**CHARCOT'S DISEASE.**—The peculiar condition known as Charcot's disease of joints may develop in the course of *tabes dorsalis* and occasionally it complicates

syringomyelia, so that it has been called a neuropathic arthropathy. It may develop at a fairly early stage of tabes, and usually affects the large joints of the lower limb (hip, knee, and ankle) owing to the preponderatingly lumbar distribution of the tabetic lesions in the cord. In syringomyelia it is more common in the upper limb for a similar reason. As a rule only one joint is involved. The onset is insidious, but the patient may suddenly discover that the joint is much swollen. This swelling may develop quite rapidly. The further progress is a story of destruction and disintegration until the joint may be completely disorganized and flail-like, so that a hinge joint like the knee or elbow can be moved in every direction. Although grating and crunching can be felt in the joint there is a complete and remarkable absence of pain. Sometimes the process of destruction is very rapid, reaching its maximum in the course of a few weeks, after which the disease may become stationary. The head of the femur has been known to disappear in the course of six weeks. This quickness of action, so unlike ordinary osteoarthritis, is one of the most puzzling features of the disease. The lesions are essentially degenerative and destructive, especially in the acute cases where it would appear as if some powerful solvent had dissolved away first the articular surface and then the bone, leaving a ragged stump and disconnected fragments. The synovial membrane may develop villous and polypoid tags. When the acute stage is past numerous osteophytes may form a fringe around the joint and in the capsule. It seems probable that during the stage of attrition large numbers of osteoblasts are set free in the joint cavity and become implanted in the capsule and periarticular tissues where they form new bone. The nature of the condition is very obscure. The pathology does not remotely resemble that of syphilis. It is commonly supposed to be due to loss of hypothetical trophic influences to the joint on account of the cord lesion. It appears more probable that a loss of joint sensibility which may develop both in tabes and syringomyelia exposes it to trauma and attrition which in some obscure way bring about the rapid osteoarthritis characteristic of Charcot's disease.

**HEMOPHILIC JOINT.**—In hemophilia an osteoarthritis may develop as the result of repeated hemorrhages into one of the large joints. The cartilage becomes eroded and fibrillated, the bone is exposed, periarticular osteophytes are formed, and the synovial membrane is thickened and fringed.

## TUBERCULOSIS OF THE JOINTS

Tuberculosis of the joints is a disease of children, and is usually secondary to tuberculosis of the adjacent bone. When it occurs in an adult it is more likely to be primary in the synovial membrane, infection being carried by the blood stream from some distant focus. Bone tuberculosis has a strong tendency to spread to the corresponding joint, so that bone and joint tuberculosis are commonly combined. The bone lesion is in the metaphysis close to the epiphyseal cartilage, and from there the infection spreads outward along the vessels and reaches the synovial membrane. Or it may destroy the epiphyseal cartilage, invade the epiphysis, penetrate the articular cartilage, and in this way reach the joint. Trauma is said to be a predisposing factor, but as usual this is difficult to prove. The joints commonly affected are the hip and knee, followed by elbow, shoulder, and ankle.

**LESIONS.**—All the joint structures and the adjacent bone are involved if the disease is not arrested, but in the adult the main lesion may be a tuberculous synovitis for a considerable time. The *synovial membrane* may resemble that of rheumatoid (infective) arthritis, but is even thicker and more voluminous, so that it may fill the entire cavity. It is gray in

color and may show tubercles on the surface or only when the mass is incised. (Plate XXXI.) Gelatinous degeneration is common and caseation may occur in the late stages. Microscopically it usually presents a classical picture of tuberculous granulation tissue with epithelioid tubercles and numerous giant cells. The *fluid* is usually scanty but highly fibrinous, so that it contains flakes of fibrin which may develop into foreign bodies known as *melon-seed bodies* or *rice bodies*. Occasionally there is abundant serous effusion (hydrops) with comparatively little synovial thickening; in these cases there may be large numbers of melon-seed bodies. The *articular cartilage* is attacked both from above and below, just as in rheumatoid arthritis. The synovial membrane, or rather the granulation tissue into which it is converted, creeps over the articular surface, becomes adherent to it, and sends vessels into it, so that the cartilage becomes eaten away and the underlying bone is exposed. (Fig. 535.) The cartilage is

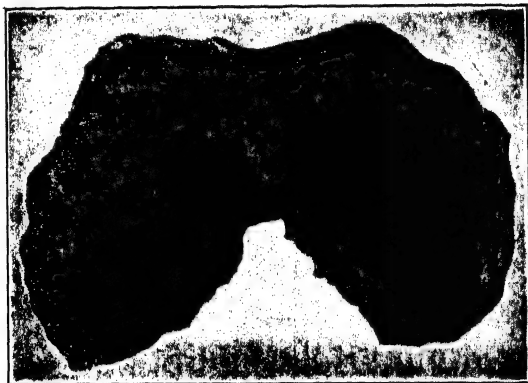


FIG. 535.—Tuberculosis of the knee joint. The articular cartilage of the femur is eaten away and the underlying bone is eroded.

also attacked by granulation tissue from below, and instead of being eaten away it may become separated in flakes or even as a complete cast of the articular surface. The *bone* shows the rarefying osteitis which has already been studied in connection with tuberculosis of bone. The initial lesion is in the red marrow, and the absorption of bone is really secondary. The *periarticular soft parts* are involved later. The ligaments are softened and finally destroyed, so that the joint may be dislocated. The muscles and other periarticular tissues undergo gelatinous degeneration, a change which is largely responsible for the *white swelling* so characteristic of tuberculous arthritis. When the gelatinous tissue undergoes caseation and liquefaction a tuberculous abscess (cold abscess) is formed, the contents of which are not true pus but liquefied necrotic tissue. If this is open or perforates the skin, the whole picture is changed, and mixed infection runs riot through all the tissues in and around the joint. *Caries sicca* is a rare form of the disease which usually affects the shoulder joint and pursues a slow course with no effusion, quiet absorption of the bone, and the formation of dense fibrous adhesions.

PLATE XXXI



Tuberculous Arthritis

*(Boyd's Surgical Pathology, courtesy of W. B. Saunders Company.)*



The termination is very variable. At almost any stage the disease may be arrested. This may result in mere stiffness, but when the articular surface is destroyed there will be fibrous or bony ankylosis. Amyloid disease may complicate prolonged secondary infection, or general miliary tuberculosis may terminate the picture.

**THE RELATION OF SYMPTOMS TO LESIONS.**—Pain, an early and constant symptom, is due to erosion of the articular cartilage. It is worse when the patient drops off to sleep, because then the watchful muscles which hold the joint rigid are off their guard. The joint is swollen and has a characteristic fusiform contour. Much of the enlargement is caused by the swelling of the synovial membrane, but in the later stages the gelatinous swelling of the periarticular soft tissues plays a part. Limitation of movement, the earliest physical sign, is a natural sequel to any inflammatory lesion in a joint. Muscular spasm is an attempt to keep the part at rest. Early atrophy of the surrounding muscles is partly due to disuse, but part of it may be due to the action of toxins.



FIG. 536.—Melon-seed bodies in a joint.

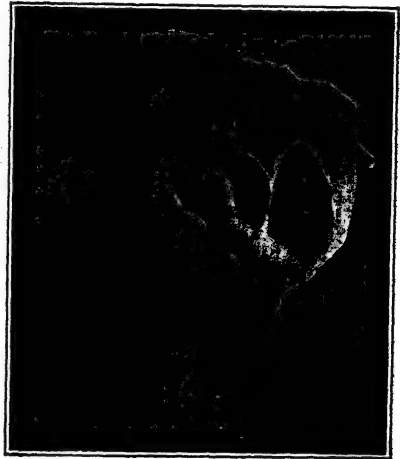


FIG. 537.—Cyst of external semilunar cartilage.

**GONORRHEAL ARTHRITIS.**—This form of arthritis occurs in about 2 per cent of cases of gonorrhea. The infection is due to spread by the blood stream. The joint infection usually occurs about the end of the third week, but it may not set in for some months after the original urethral infection. The disease is a polyarthritis, but it is usually confined to a few of the large joints, of which the knee is the most frequent sufferer. The arthritis may be acute or chronic.

**LOOSE BODIES IN THE JOINTS.**—Three forms of loose bodies in joints may be found in such conditions as tuberculosis, osteoarthritis and Charcot's disease, and loose bodies may occasionally occur in an apparently normal joint. These three varieties are fibrinous bodies, fibrous and fatty bodies, and cartilaginous bodies. (1) *Fibrinous loose bodies* occur chiefly in tuberculous joints, and also in synovial sheaths and bursæ affected by tuberculosis. They take the form of small, round or oval bodies like melon-seeds or rice-grains, and may be present in large numbers (Fig. 536). It is difficult to say if they are formed as the result of some fibrinous change on the surface of the synovial membrane or if they are deposited from fluid

rich in fibrin. (2) *Fibrous and fatty loose bodies* are formed from villous tags of synovial membrane which become detached in tuberculous arthritis and osteoarthritis, in both of which conditions the membrane is often marked by numerous fringes. Some of the bodies may still be attached by a slender pedicle. (3) *Cartilaginous loose bodies* may arise in three different ways. (a) A cartilaginous osteophyte may be detached in osteoarthritis and particularly in Charcot's disease. (b) A loose body occurring in an otherwise normal joint has always been a puzzling phenomenon, but it appears probable that it is a fragment of articular cartilage which has become detached as the result of direct trauma or of muscular or ligamentous strain. (c) Synovial chondromata may develop in tags of synovial membrane and become detached.

**CYSTS CONNECTED WITH JOINTS.**—The cyst may or may not communicate with a joint. A cyst in the neighborhood of a joint is likely to fall into one of three groups. (1) *Cysts due to distention of a bursal sac* which may or may not normally open into the joint cavity. (2) Cysts formed by hernial protrusion of the synovial membrane through gaps in the capsular ligaments. Such a cyst is called a *Baker's cyst*, which almost always develops in connection with the knee, appears in the popliteal space, and may make its way down the leg after the manner of a cold abscess. (3) *Cysts of the semilunar cartilages* of the knee, usually the external, occasionally the internal. (Fig. 537). The cyst is multilocular, the contents are gelatinous, and a preceding history of trauma is common. Some of the cysts may have an endothelial-like lining. The lesion appears to be the result of a gelatinous degeneration of the fibro-cartilage with cyst formation, so that the pathogenesis is similar to that of ganglion (page 941). The cyst lining is probably formed by modified fibroblasts. Some writers believe that the cysts are developmental in character, arising from portions of the synovial membrane included in the semilunar cartilage.

## TUMORS OF SYNOVIAL MEMBRANE

**SYNOVIAL GIANT-CELL TUMORS.**—Giant-cell tumors may arise from the synovial membrane of tendon sheaths, particularly those of the fingers and thumb, and of joints. They are commoner in women. They form golden or reddish-brown nodular masses with yellow or red areas on the cut surface. Microscopically they resemble the lesions of villo-nodular synovitis, and seem to be inflammatory rather than neoplastic in nature. They may be highly cellular or mainly fibrous, depending on the stage of development. A characteristic feature is the presence of numerous lipid-filled histiocytes which give the lesion its yellow color. The giant-cells may also contain lipid and iron pigment. There may be traces of villi, and the slit-like clefts and spaces characteristic of synovioma may be present.

**PIGMENTED VILLO-NODULAR SYNOVITIS.**—This is the name given by Jaffe and his associates to bearded villous or nodular masses which occur principally in the knee and the tendon sheaths of the hand. They consist at first of folds and villi of synovial membrane with vascular and edematous granulation tissue, which later become more fibrous and fuse together to form a compact mass. They are composed of the same lipid-filled histiocytes, giant-cells and blood pigment already described in giant-cell tumors of synovial membrane. Indeed all stages seem to exist between this form of synovitis, the giant-cell tumors and the histiocytomas of the skin known as dermatofibroma and sclerosing hemangioma (Spencer and Whimster).

## LESIONS OF THE INTERVERTEBRAL DISCS

Interest in the pathology of the intervertebral discs dates from the work of Schmorl of Dresden in 1925. Each disc consists of: (1) the

nucleus pulposus, a highly elastic semi-fluid mass compressed like a spring between the vertebral surfaces; (2) the annulus fibrosus which surrounds and confines the turgid nucleus; (3) the cartilage plate which separates the nucleus from the vertebral body. Lesions may develop in any of the three constituents. Owing to man's upright position the discs are subjected to constant strain for which they were not originally intended, so that degeneration in later life is commoner than in any other organ, with corresponding loss of the normal cushioning function. The three chief pathological conditions related to the discs are herniation, posterior displacement, and spinal deformity.

*Herniation of the nucleus pulposus* into the spongiosa of the vertebral bodies may be due to lesions of the cartilage plate or the bone. As the result of tearing of the cartilage plate (as in compression fracture) or degeneration of the plate due to age the turgid nucleus bulges into the body of the vertebra. Osteoporosis of the vertebræ allows multiple protrusions to occur. These lesions, which are known as Schmorl's nodes, are very common and usually of no clinical significance.

*Posterior displacement* of the nucleus into the spinal canal, commonly called *prolapse*, is due to degeneration of or injury to the annulus fibrosus. In the past the prolapsed disc has been mistaken for chondroma or myxofibroma. As a rule the prolapse causes no symptoms, but when it occurs between the fifth lumbar vertebra and the sacrum or between the fourth and fifth lumbar vertebræ it may press on the fifth lumbar or first sacral nerve roots causing first low back pain and later sciatica. The symptoms are relieved by removal of the displaced portion of disc.

*Spinal deformities* related to disc pathology fall into three groups: (1) juvenile kyphosis, (2) senile kyphosis, and (3) spondylitis deformans. *Juvenile or adolescent kyphosis* occurs in boys, and is associated with a series of prolapses of nucleus pulposus through ruptured cartilage plates, probably due to congenital weakness of the plates. There is loss of disc substance most marked anteriorly, with consequent pressure in that area and interference with growth, so that the vertebræ become wedge-shaped and kyphosis results. *Senile kyphosis* is caused by degeneration and destruction of the anterior part of the discs. *Spondylitis deformans* usually takes the form of osteoarthritis of the spine, the typical senile spinal disease. Degeneration of the annulus allows the discs to press on the intervertebral ligaments, thus exerting a pull on the periosteum to which the ligaments are attached. The continued pull leads to overgrowth of the bone at the margins of the vertebræ with the formation of osteophytes, lipping, and limitation of movement. In the Marie-Strümpell type of spondylitis the discs are converted into bone and fuse with the bodies of the vertebræ; the result is complete rigidity, the poker back.

#### ADDITIONAL READING

**Anchylosing Spondylitis.** ROMANUS: Pelvo-Spondylitis Ossificans in the Male and Genito-Urinary Infection. Stockholm, 1953.

**General References.** COLLINS: The Pathology of Articular and Spinal Diseases, London, 1949.

**Heberden's Nodes.** NACHLAS: Arch. Surg., 1932, 25, 1067.

**Hypertrophic Osteoarthropathy.** LOCKE: Arch. Int. Med., 1915, 15, 659. PATERSON: Brit. J. Radiol., 1927, 32, 435.

- Intervertebral Discs.** BEADLE: Gt. Brit. Med. Res. Council, Spec. Rep. Series, No. 161, London, 1931. BRADFORD AND SPURLING: The Intervertebral Disc, Springfield, Ill., 1941. DONOHUE: Am. J. Med. Sci., 1939, **98**, 419. GEIST: J. A. M. A., 1931, **96**, 1676. SCHMORL: Klin. Wchnschr., 1929, **8**, 1243.
- Lesions of Muscle in Rheumatoid Arthritis.** OGRYZLO: Arch. Path., 1948, **46**, 301.
- Loose Bodies.** FISHER: Brit. J. Surg., 1921, **8**, 493.
- Osteoarthritis.** CALLENDER AND KELSER: Am. J. Path., 1938, **14**, 253. FISHER: Brit. J. Surg., 1922, **10**, 52. KEEFER, *et al.*: Arch. Int. Med., 1934, **53**, 325. PARKER, *et al.*: Arch. Path., 1934, **17**, 516.
- Pigmented Villo-nodular Synovitis.** JAFFE, LICHTENSTEIN and SUTRO: Arch. Path., 1941, **31**, 731. SPENCER and WHIMSTER: J. Path. & Bact., 1950, **62**, 411.
- Rheumatoid Arthritis.** ASBOE-HANSEN: Ann. Rheum. Dis., 1950, **9**, 149. BAGGENSTOSS AND ROSENBERG: Arch. Int. Med., 1941, **67**, 241; Arch. Path., 1943, **35**, 503. FREUND, *et al.*: Am. J. Path., 1942, **18**, 865. HOLLANDER, *et al.*: Comroe's Arthritis and Allied Conditions, Philadelphia, 1952. PEARSE: Lancet, 1950, **1**, 954. SHERMAN: Bull. Hosp. for Joint Dis., 1951, **12**, 110. STEINER, *et al.*: Am. J. Path., 1946, **22**, 103.
- Semilunar Cartilage Cysts.** OLLERENSHAW: Brit. J. Surg., 1929, **16**, 555. ZADEK AND JAFFE: Arch. Surg., 1927, **15**, 677.
- Synovial Sarcoma.** DE SANTO, *et al.*: Surg., Gynec. and Obst., 1941, **72**, 951.
- Tuberculosis.** FRASER: Tuberculosis of the Bones and Joints in Children, Edinburgh, 1914. PHEMISTER: J. Bone and Joint Surg., 1925, **7**, 835.

## THE MUSCLES, TENDONS, AND BURSÆ

THERE are some points in connection with the histology of muscle which must be kept in mind, else normal appearances may be mistaken for the lesions of disease. If fresh muscle newly removed from the living body, as in a surgical operation, is at once placed in a fixative such as formalin, the fibers may appear wavy and distorted, and the contents are broken up so that part of a fiber may present an appearance of a hyaline structureless lump, while another part appears empty. These changes are due to the contractility of the fiber, and they can be obviated by keeping the muscle in the ice-box, as is done with autopsy material. For differences in the finer histological detail before and after rigor mortis as shown by special muscle stains, Miller's paper may be consulted.

The voluntary muscles are seldom the seat of pathological processes. Those which do occur may be divided as follows: (1) atrophic changes, (2) degenerative changes, (3) inflammatory changes, (4) fibrotic changes, and (5) tumors. A muscle consists of interstitial connective tissue as well as muscle fibers, and much of the pathological change affects this tissue.

**Atrophic Changes.**—Atrophy of a muscle may be due to disuse, to joint disease or to nerve lesions. (1) The *atrophy of disuse* is a commonplace observation. The fibers shrink in size, and if the disuse is permanent the contractile substance may be converted into fibrous and fatty tissue. (2) The *atrophy which accompanies chronic disease of a joint, e. g., tuberculosis or rheumatoid arthritis*, is partly due to disuse, but the atrophy may be so extreme that it seems probable that some other factor must play a part. This may be a local toxic action, or sensory impressions may pass from the diseased joint to the cord and there induce changes in the motor cells of the anterior horn. (3) *Neuropathic atrophy* is seen in injuries of motor nerves, acute poliomyelitis, and progressive muscular atrophy. It is evident that in all these conditions disuse will play a part in producing the atrophy, but in addition there may be a loss of hypothetical trophic impulses to the muscles. The electrical "reaction of degeneration" is present in these cases.

**Degenerative Changes.**—As long ago as 1863, Zenker described the degeneration of muscle in typhoid fever which goes by his name. Zenker's degeneration is a hyaline change, most commonly seen in the rectus abdominis and the muscles of the abdominal wall, but also in the diaphragm and the voluntary muscles elsewhere. A similar change may complicate the pneumonia of epidemic influenza and that following epidemic measles, but in these cases the change is confined to the rectus abdominis. The affected part of the muscle becomes pale, undergoes a massive hyaline

degeneration, as a result of which it becomes remarkably fragile, so that rupture is common, and this may be accompanied by hemorrhage and the formation of a hematoma. If organisms are circulating in the blood, they may infect the hematoma and cause abscess formation in the abdominal wall. *Microscopically*, the first change is a hyaline swelling of the contractile substance, followed shortly by a remarkable nuclear proliferation, the new cells sometimes filling the sarcolemma sheath, and being concerned with the removal of the degenerated muscle. There is rapid loss of the transverse and longitudinal striations, and the fiber becomes amorphous, homogeneous, and highly refractile. Vacuoles may appear in the fiber, and the hyaline material may become granular.

*Regeneration* of muscle after this hyaline degeneration may be remarkably complete, and the entire muscle may be renewed. The hyaline clumps become surrounded by phagocytes which fill the sarcolemma and remove the débris. At the same time the remaining muscle nuclei of the old fibers multiply and produce new muscle cells. This complete regeneration is not seen in wounds of muscle, especially where a piece has been excised. In such a case there is partial regeneration at the edge of the gap, but most of the union is due to fibrous tissue.

**INFLAMMATORY CHANGES.**—Acute inflammation of muscle is not common. It affects the interstitial tissue, with secondary destruction of the muscle fibers. The infection may spread from a suppurating wound, or small abscesses may be formed in the muscle in the course of pyemia. In rare cases an *acute suppurative myositis* appears in an otherwise healthy patient, a condition analogous to acute osteomyelitis in a bone. Here the inflammation is limited to a single muscle, the pus being confined within the sheath of the muscle. *Acute polymyositis* is a rare form of severe non-suppurative inflammation of many muscles of unknown origin. The muscles are hard, swollen, and extremely painful and tender. They show round-cell infiltration with areas of liquefaction. Tuberculosis, syphilis and actinomycosis may in rare cases produce in muscles the lesions characteristic of those infections. The inflammatory lesions caused by trichiniasis are described elsewhere. A rare condition easily mistaken for trichiniasis is *dermatomyositis*, a non-purulent myositis associated with inflammation of the skin. The skin, subcutaneous tissue and muscle are edematous and infiltrated with lymphocytes and plasma cells. There is tenderness, pain on movement, and erythema of the overlying skin. The prognosis is bad.

**Fibrotic Changes.**—Under this general heading may be considered myositis ossificans, myositis fibrosa, and congenital torticollis.

**MYOSITIS OSSIFICANS.**—There are two kinds of so-called ossifying myositis, which bear no relation to one another. They are the traumatic and the progressive forms. *Traumatic myositis ossificans* is a not uncommon condition which may be the result of repeated injury to a muscle or a single severe injury, especially when accompanied by hemorrhage. A good example is the development of bone in the adductor muscles of the thigh in riders. It is possible that osteoblasts are detached as a result of the trauma and become implanted in the muscle where they form bone, but it is also possible that there may be a metaplasia of fibrous tissue into bone, especially when there has been hemorrhage and tissue destruction. The formation of bone which occasionally takes place in the edges of a

laparotomy wound might be explained on this basis. The great practical importance of the condition is the danger that it may be mistaken for an osteogenic sarcoma of bone invading the muscle.

**PROGRESSIVE MYOSITIS OSSIFICANS.**—This is a very rare progressive disease, which commences in childhood and slowly kills the patient. The first lesions take the form of doughy and sometimes painful swellings, particularly in the muscles of the back and neck. These swellings subside, leaving areas of fibrosis in which bone is gradually formed. The progress of the disease is marked by exacerbations and remissions. Large bony plates are formed, and the body may finally be enclosed in a sheath of bone which makes all movement impossible and leads to the death of the patient from respiratory paralysis. The disease appears to be some obscure disorder of the bone-forming power of the tissues, for congenital bony defects such as microdactylia in the hand and absence of a phalanx in the great toe are often present.

**PROGRESSIVE MYOSITIS FIBROSA.**—This is another very rare condition, much less well recognized than myositis ossificans, but essentially similar in nature. Many muscles of the back and upper limbs develop swellings in part or the whole of the muscle, more especially at the attachments. The swelling is hard, diffuse and painless. In a few days it decreases in size and becomes harder, and this induration is permanent. The swelling may suddenly recur, as in the case of myositis ossificans. Microscopically there is a marked general increase in the fibrous tissue of the muscle, with degeneration and disappearance of the muscle fibers. There is a notable absence of round-cell infiltration. It seems probable that the disease is identical with myositis ossificans, with the exception that in the latter disease the new-formed fibrous tissue becomes converted into bone.

**DERMATOMYOSITIS.**—This condition, which is much more an involvement of muscle than of skin, is a member of the diffuse collagen group. The skin lesions take the form of a patchy hyperemia, with edema of the ground substance, perivascular collections of chronic inflammatory cells, and hyaline thickening of the small arteries with occasional necrosis of their walls. The lesions in the striated muscles, including the heart, are very striking. Grossly they are pale and atrophic, whilst microscopically they show all degrees of change from loss of cross-striation to complete disintegration. In sections which I have studied one gets the impression that the ground substance which holds together the fibers and the individual fibrils of those fibers has become dissolved and everything is falling to pieces. At an earlier stage the fibers are swollen and hyaline. The cells of the sarcolemma may be enlarged, rounded and multinucleated, and are possibly engaged in an attempt at repair. Myelin sheath degeneration of the peripheral nerves is frequent, perhaps due to interference with the ground substance between the fibers.

**CONGENITAL TORTICOLLIS.**—Congenital torticollis may be regarded as the result of a localized form of myositis fibrosa which usually develops about the age of four years. In these cases the history goes back to the so-called "sterno-mastoid tumor of infancy," which generally appears about ten days after birth. A spindle-shaped swelling develops in the sterno-cleido-mastoid; this is peculiarly hard and feels like cartilage. The swelling persists for two or three months and is then gradually absorbed, disappearing entirely in four to six months after birth. If the muscle is now excised it is found to consist entirely of fibrous tissue with complete replacement of the muscle fibers. The neck lengthens rapidly in the fourth year, and as the fibrosed muscle is unable to grow, the head is pulled over to that side—a condition of congenital torticollis. Middleton has shown that the sterno-cleido-mastoid tumor is produced as the result of acute venous obstruction due to pressure on the veins during labor, rendered permanent by the thrombosis of the veins. When the artery to a muscle is tied experimentally or the artery and vein together, the result is

simple atrophy. But when the vein above is tied, the arterial supply being left intact, the muscle becomes acutely swollen, hard and tender, and very cyanosed. The fibers disintegrate and the muscle is densely infiltrated with round cells. In the course of a few months such a muscle is completely replaced by fibrous tissue. When the vein alone is obstructed the autolytic products from the breaking down muscle fibers are not carried away from the part and appear to stimulate proliferation of fibroblasts. The marked edema of the muscle also favors the formation of fibrous tissue.

**DUPUYTREN'S CONTRACTION.**—Owing to thickening, hardening and shortening of the palmar fascia the fingers may become progressively flexed on the palm, so that normal use of the hand is impossible. The etiology is unknown. The microscopic picture is one of active proliferation of fibroblasts which may be mistaken for fibrosarcoma, with dense collagen formation.

**VOLKMANN'S CONTRACTURE.**—This condition, called originally by Volkmann ischemic contracture, usually occurs in young people and affects the muscles of the forearm. It is commonly associated with the pressure of splints or a tourniquet or with hemorrhage resulting from a fracture. Within a few hours of the receipt of injury burning pain develops in the hand or forearm. This is followed by contracture of the fingers which become fixed in the flexed position. If the muscle is exposed when the condition is fully developed it is hard, homogeneous, yellowish in color and is not recognizable as skeletal muscle. Microscopically the nuclei and cross-striations are lost, there may be an infiltration of inflammatory cells and phagocytes at the margin of the area, and the picture is one of infarct, similar to that of a cardiac infarct. Later the part becomes fibrosed.

Volkmann originally (1872) believed that the cause of the condition was direct pressure on the arteries. In 1914 the ischemic theory was given up, and the view substituted that venous obstruction was the causal factor (J. B. Murphy). A return has now been made to the idea that the condition is essentially ischemic in nature, due usually to arterial spasm resulting from injury to the wall of the vessel (Griffiths). An identical picture, both pathological and clinical, can be produced in the rabbit by ligating the arteries to a limb.

**FIBROSITIS.**—Reference may be made in this place to the subject of fibrositis, commonly called muscular rheumatism. In this condition chronic inflammatory foci are found not only in the muscles, but also in the subcutaneous tissues, nerve sheaths, periarticular structures, etc. At first there is an acute inflammatory edema with swelling of the connective-tissue fibers; the center of the lesion may be necrotic. Any cellular exudate is slight and lymphocytic in type; polymorphonuclears are absent. The tension caused by the localized edema irritates the nerve endings, and muscular movement (as in sciatica, stiff neck, etc.) may be accompanied by intense pain. Many of these lesions are now believed to be psychogenic in origin, and are attributed to strain and tension which makes the muscles tense as if continually contracted.

**ANTERIOR TIBIAL SYNDROME.**—A condition similar to Volkmann's contracture is the massive ischemic necrosis with replacement fibrosis which involves the muscles of the anterior tibial compartment of the leg. There is a history of unaccustomed strenuous exercise of the limb, such as kicking a football. Occasionally there has been injury to parts of the body other than the affected limb. There may be evidence of involvement of the anterior tibial nerve (Carter). Owing to unaccustomed exertion the muscles are injured with rupture of some fibers and intramuscular hæmorrhage which can be demonstrated by biopsy. Even prolonged activity of a muscle can cause a 20 per cent increase in its bulk owing to accumulation of fluid in the tissue spaces. The anterior tibial compartment has rigid walls, and the increased pressure causes pressure on the veins and venous stasis. This



intensifies the swelling, and finally the pressure leads to occlusion of the arteries with resulting ischemic necrosis.

**TUMORS.**—Tumors of striated muscle, either primary or secondary, are remarkably rare. Primary tumors may be myoblastoma or rhabdomyoma. *Myoblastoma*, usually called granular cell myoblastoma, is described on page 257. It is there pointed out that this tumor may be really neurogenic in origin, so that the term myoblastoma is misleading. It is well known that the lesion is found in sites devoid of striated muscle as well as in the substance of such muscle. *Rhabdomyoma* consists of fully striated fibers. It occurs in the heart, bladder, vagina and cervix, and is highly malignant. On mucous surfaces, such as bladder and vagina, it tends to be lobulated and polypoid.

**MYASTHENIA GRAVIS.**—This rare and mysterious disease is characterized by great weakness, most marked in the muscles of the face, but shared to a lesser degree by the other muscles. Nothing is found in the affected muscles or in the nervous system to account for the myasthenia. It is true that the muscles show a marked degree of infiltration with small round cells, but there is no atrophy of the fibers, and similar infiltrations of small cells are found in the liver, adrenals and other organs. The meaning of these infiltrations is quite obscure, but there is hyperplasia of the thymus in 50 per cent of the cases. Definite thymomas have been described, and there may be thyroid hyperplasia. All this suggests a possible endocrine basis for the disease. The myoneural junction is the probable seat of the trouble. Normal excitation transmission at this junction depends on the liberation of acetylcholine, and probably is conditioned by endocrine activity. Prostigmine acts on the myoneural junction, and is very valuable in treatment of the disease. The occasional association of thymic tumors with myasthenia gravis suggested to Blalock the possibility that removal of the thymus, even though no tumor was present, might be beneficial, a hope which has been abundantly satisfied. A number of the cases recovered so completely that it was possible to discontinue the prostigmine.

## THE TENDONS

**Tenosynovitis.**—The tendons are non-vascular and therefore immune to inflammation, but the tendon sheaths at the wrist and ankle are often infected. All the usual forms of inflammation are met with in the tendon sheaths. *Traumatic tenosynovitis* occurs in piano players, typists, and others whose tendons are subjected to excessive use. Fibrin is laid down on the wall of the sheath and the surface of the tendon, so that cracking is felt when the tendon is used. If effusion occurs, an elongated swelling appears in the line of the tendon. *Suppurative tenosynovitis* may result from spread of infection from a septic process in the fingers. *Gonorrheal tenosynovitis* may be dry, serous, or suppurative. *Tuberculous tenosynovitis* resembles tuberculous arthritis. There may be an abundant formation of tuberculous granulation tissue causing a "white swelling" like that seen in tuberculosis of a joint. Or there may be abundant serous effusion (hydrops) with only limited production of granulation tissue, but abundant deposits of fibrin which are rubbed off by the play of the tendon, so that large numbers of melon-seed bodies are formed.

**Ganglion.**—This is a cystic swelling which develops in connection with a tendon sheath. The common position is the back of the wrist, but it may occur on the back of the foot and rarely on the outer aspect of the knee. It is attached to the tendon sheath or the joint capsule, but does

not communicate with these cavities. It appears to commence as a proliferation of the connective tissue of the sheath; this undergoes mucoid degeneration with the formation of numerous small cysts which fuse to form one large cyst filled with soft mucoid material. Although we have spoken of a cyst, it is not a true cyst, for there is no endothelial lining. The condition known clinically as *compound palmar ganglion* is a tuberculous tenosynovitis.

### THE BURSÆ

A bursa, which is a sac lined by synovial membrane and containing synovial fluid, may be the seat of inflammation or tuberculosis. *Traumatic bursitis* is usually caused by chronic and repeated irritation ("housemaid's knee," "student's elbow"), but occasionally it is due to a blow. The bursa is distended with serous fluid (hydrops), and in course of time the wall becomes thickened and covered with ridges and tags. The latter may be detached, forming melon-seed bodies. *Infective bursitis* is caused by a perforating wound or direct spread of infection from the adjacent joint. *Tuberculous bursitis* may take the form of hydrops with melon-seed bodies, or the bursa may be filled with granulation tissue, which eventually undergoes softening and liquefaction.

### ADDITIONAL READING

- Anterior Tibial Syndrome.** CARTER, *et al.*: *Lancet*, 1949, 2, 928.  
**Degeneration and Regeneration of Muscle.** FORBES: *Arch. Path.*, 1926, 2, 318, 486.  
**Dupuytren's Contracture.** MEYERDING, *et al.*: *Surg., Gynec. and Obst.*, 1941, 72, 582.  
**Ganglion.** KING: *J. Path. and Bact.*, 1935, 41, 117.  
**Histology of Muscle.** MILLER: *J. Path. and Bact.*, 1933, 37, 127.  
**Myasthenia Gravis.** MILLER: *Arch. Path.*, 1940, 29, 212.  
**Myoblastoma.** CRANE AND TREMBLAY: *Am. J. Path.*, 1945, 21, 357.  
**Myositis Fibrosa.** PRICE: *Brit. Med. J.*, 1930, 1, 1131.  
**Progressive Myositis Ossificans.** MAIR: *Edinburgh Med. J.*, 1932, 39, 13.  
**Torticollis.** MIDDLETON: *Brit. J. Surg.*, 1930, 18, 188.  
**Tumors of Muscle.** CAPPELL AND MONTGOMERY: *J. Path. and Bact.*, 1937, 44, 517.  
 KLEMPERER: *Am. J. Cancer*, 1934, 20, 324.  
**Volkmann's Contracture.** GRIFFITHS: *Brit. J. Surg.*, 1940-41, 28, 239. MURPHY: *J. A. M. A.*, 1914, 63, 1249.

## Chapter

## 35

### THE SKIN

THE skin is a very remarkable structure. It is moist, supple, elastic and durable. The cells of the epidermis are continually multiplying, but the epidermis itself does not increase in thickness, because the surface cells are dying and dead though remaining united to one another like tiles on a roof, tiles which are continually blown away by the wind and continually replaced by new ones. The living cells are shielded by the very thin but tenacious film of dead cells against extremes of heat and cold, trauma, bacteria and viruses. This film is continually kept in good condition by the secretions poured out by the glands of the skin. Despite its thinness (on the forehead the epidermis is only 0.06 mm. thick) the skin effectively protects the delicate internal structures and fluids and forms the almost perfectly fortified frontier of a closed world. Just as the cerebrospinal fluid is a mirror in which are reflected many disorders of the central nervous system, so the skin mirrors sickness and health, youth and age, due in large part to changes in the physical state of the mucopolysaccharides of its ground substance.

In structure seemingly simple, although in reality complex, the skin appears to surpass even the liver in the multiplicity of its functions. In addition to its protective function it controls the fluid content of the tissues, it is an efficient insulator and heat regulator, it both synthesizes cholesterol and converts it into vitamin D, it is the most extensive and varied of the sense organs, and it is one of the most important immunological structures, being a prime producer of antibodies.

The skin is the largest organ of the body, constituting 16 per cent of body weight in the adult and covering 19,000 square centimeters; it is the most readily observed; it is the most accessible for biopsy, and yet until recently the study of its lesions have been largely left by the general pathologist to the specialist in skin pathology. In previous editions of this book there was no chapter on the skin.

**Normal Histology.**—The skin consists of epidermis, dermis and epidermal appendages. Pathological lesions may develop in one or more of these elements. The *epidermis* consists of four layers: (1) a basal layer of single cells, with hyperchromatic nuclei which normally show a few mitoses indicating the activity of growth, the mitoses being more abundant when the biopsy is taken during the night, when growth is rapid; (2) a thick prickly-cell layer, the rete malpighii; (3) a thin granular layer consisting of diamond-shaped cells filled with granules; and (4) a surface layer, the stratum corneum, consisting of dead keratinized cells which have lost their nuclei. In the palms and soles there is in addition a stratum lucidum

composed of several layers of clear cells without nuclei. Interspersed among the basal cells are dendritic cells, the melanoblasts (melanocytes) whose function it is to form melanin. Some of these cells contain melanin pigment, others do not. The amount of pigment varies greatly with varying conditions. The function of melanin is to protect the body against the actinic rays of ultraviolet light.

The *dermis* or *corium* projects into the epidermis as dermal papillæ which alternate with downward projections of epidermis, the rete pegs. The dermal papillæ vary greatly under conditions of disease as to length, width, vascularity, fluid content and density of collagen. It is in the dermis that the true gel-like character of the ground substance was first recognized. This is the mucopolysaccharide, hyaluronic acid, on which so much of the physical character of the skin depends. The hyaluronic acid is acted on (depolymerized) by the enzyme hyaluronidase, which is, therefore, a spreading factor that governs the permeability of the skin. An increase of permeability will facilitate the spread of chemicals, bacteria and viruses. The permeability is under endocrine control, being decreased by estrogens and increased by cortisone.

The *epidermal appendages* are the sweat and sebaceous glands, the hair follicles and nails. The *sweat glands* open for the most part on the surface. The secretory coiled part lies in the dermis and is lined by cuboidal cells, external to which there is a layer of flattened contractile myoepithelial cells. The secretion is thin and watery. It may be of interest to note that sweat glands are only numerous in mules, donkeys and humans. The sweat glands in the axilla, groin, nipple and genital region are known as apocrine glands, because part of the cytoplasm is separated during secretion (*apo*, from and *krino*, I separate). They are much larger than the ordinary sweat glands (eccrine glands), and are lined by tall columnar cells, the cytoplasm of which is markedly acidophilic. Their ducts are usually connected with hair follicles. The *sebaceous glands* arise for the most part from the hair follicles to which they are attached. The cells become converted into fatty material which is liberated as secretion with total destruction of the cells (holocrine gland). Lesions which are greasy in character due to overactivity of the sebaceous glands are described as seborrheic in character. Or the secretion may be drier and mixed with exfoliated cells from the ducts and follicles, in which case it will form crusts. As sebaceous glands are filled with fatty material, fat-soluble chemicals and oils can penetrate the epidermal barrier via their ducts and reach the dermis. On the other hand the fatty secretion on the surface serves to protect the underlying living cells from bacteria and water-soluble poisons. The *arrector pili* smooth muscles are attached to the hair follicles. Contraction of these muscles causes the hairs to be erected and expels the sebaceous secretion.

When the histopathologist studies a section of the skin he looks first at the epidermis as a whole to determine its thickness, and then in turn at the various layers of the epidermis for changes in quality and quantity, at the rete pegs, at the dermal papillæ, the dermis and the epidermal appendages.

**Definition of Terms.**—Certain expressions are in common use in skin pathology and need to be defined. Acanthosis (*akantha*, a spine or thorn), is a hyperplastic thickening of the prickle-cell layer, the rete malpighii. *Spongiosis* signifies intercellular edema in the rete malpighii, and is usually associated with acanthosis owing to increased nutrition of the rete cells. *Hyperkeratosis* is thickening of the stratum corneum. It is associated with increase in thickness of the stratum granulosum. *Parakeratosis* signifies imperfect keratinization with retention of nuclei in the horny layer, and is associated with loss of the granular layer. *Dyskeratosis* is a term applied to changes in the epidermis suggestive of developing malignancy, *e. g.* hyperchromatism, loss of cell polarity and increase in the number of mitoses, changes which may be summed up in two descriptive words, atypicality and jumbling, the latter referring to loss of the normal orderly cell arrangement.

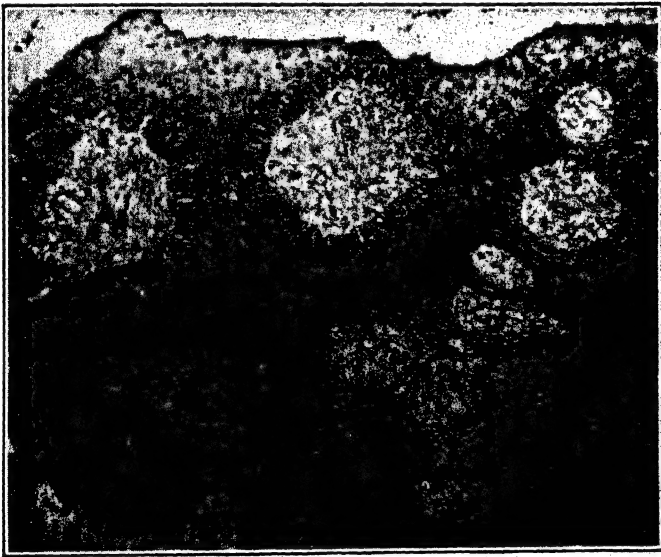


FIG. 538.—Artefact. Owing to tangential cutting the dermal papillæ appear to be embedded in the epidermis.  $\times 110$

No attempt will be made in this place to give an account of the innumerable conditions which have been described and named as skin diseases of which there are over 300. Attention will be confined mainly to those lesions in which skin biopsy with microscopic examination may be of diagnostic value. The microscopic examination of minute pieces of skin is an art which requires much experience. The difference between lesions may be quantitative rather than qualitative, and such terms as cellular infiltration, edema, acanthosis and dyskeratosis are continually recurring. The taking of the biopsy specimen is important, for it may be very difficult for the pathologist to orientate the tiny lesion properly. The surgeon should place the tissue with the cut surface downward on a piece of blotting paper.

The specimen is transfixed with a hypodermic wire stilette which remains as a marker up to the time of embedding. This prevents confusing artefacts due to tangential cutting such as are shown in Figure 538.

The lesions to be discussed will be considered under the headings of (1) hyperplasias, (2) pigment disturbances, (3) nonspecific inflammations, (4) specific inflammations, (5) neoplasms, (6) cysts, and (7) cutaneous manifestations of systemic disorders. It will soon become apparent that this rigid compartmentation is artificial and cannot always be maintained.

## HYPERPLASIAS

**Verruca Vulgaris.**—The common wart is the result of invasion of the epithelial cells by a specific virus. It is a disease principally of adolescence and early adult life affecting particularly the fingers, palm and forearm.



FIG. 539.—Verruca vulgaris. Papillary acanthosis and hyperkeratosis are marked.

The warts occur in crops owing to autoinoculation. A particularly troublesome variety is the plantar wart, which causes painful pressure on the sensory nerve endings. This lesion occurs at pressure points on the sole, the commonest site being under the head of the second metatarsal. It must not be confused with a corn. The *microscopic changes* are papillary acanthosis with marked hyperkeratosis, an unusual degree of parakeratosis so that many nuclei can be seen in the stratum corneum, vacuolization of the cells of the rete and widening of the rete pegs. (Fig. 539.) The cells are swollen and mitoses are numerous. Intracellular bodies are usually present which may be interpreted either as ker-

atotic degeneration or as true cytoplasmic inclusions.

Certain warts from the hands and feet differ clinically from other warts from the same sites in that they have a smooth margin, relatively less keratinization, and a surrounding erythematous halo. Suspensions of these warts yield virus-like particles under the electron microscope. They also possess eopinophilic intranuclear inclusion bodies and characteristic vacuolated cytoplasmic masses (Bunting *et al.*).

**CALLUS AND CORN.**—In both of these lesions there is hyperkeratosis with marked thickening of the stratum corneum. In the corn or clavus keratinization is developed as a dense localized plug.

**ACANTHOSIS NIGRICANS.**—The lesions are dark colored and warty in character, usually in the axilla, groin, elbows and knees. In adults there is a peculiar and unexplained association with abdominal cancer. The *microscopic appearance* is indicated by the descriptive name. The acanthosis takes a papillary form, accounting for the warty appearance, and hyperkeratosis is often more marked than acan-

thosis. The most characteristic feature is a dense melanin pigmentation of the basal layer of cells of the epidermis.

**ICHTHYOSIS.**—The name, which means fish skin, is highly appropriate, for the surface is covered with large lamellæ resembling fish scales. Most cases are congenital. *Microscopically* the disease is another example of hyperkeratosis in extreme form, with thinning of the rete malpighii and absence of the granular layer, thus reversing the usual relationship of the granular and horny layers.

**Seborrheic Keratosis.**—This hyperplasia is also known as senile wart (*verruca senilis*) and basal cell papilloma. The condition is one of the most important in dermatological pathology, for it is common, it is frequently mistaken by the clinician for a pigmented mole or melanoma, and by the



FIG. 540.—Seborrheic keratosis. Extreme hyperkeratosis on surface and keratotic plugs in depths of epidermis.  $\times 45$ .

inexperienced pathologist for a basal cell carcinoma. The lesions, often in large numbers, occur on exposed parts of the body usually in persons over middle age. They are small, raised and wart-like, frequently pigmented to a marked degree, and the soft, greasy surface is responsible for the descriptive term seborrheic (*sebum*, tallow, *rhoia*, a flow). They have been likened to a piece of gum stuck on the surface.

The *microscopic appearance* is distinctive, but it is singularly difficult to present a word picture or convey a correct impression of this appearance. The lesion is entirely epidermal, which differentiates it from the common intradermal nevus. The sharply delimited patch of thickened epidermis gives an appearance of being "stuck on" when the slide is held up to the light. There is a marked degree of acanthosis, but the lower limit of the thickened rete malpighii is level, in sharp contrast to the downgrowths so

characteristic of basal cell carcinoma. A subtle change has overtaken the various layers of the rete, for the cells have now a curious uniformity, giving at first glance a suggestion of basal cells, but on closer scrutiny being clearly of the prickle-cell variety. Even the basal layer has lost its usual characteristics. On the surface there may be a marked degree of hyperkeratosis (Fig. 540), but the hyperkeratotic material has often been desquamated, so that the descriptive title may appear to be unjustified. Perhaps the most arresting feature is the formation of sharply demarcated eosinophilic nests or plugs of laminated keratin at different levels of the rete, giving an impression of an inverted papilloma. This must on no account be mistaken for epidermoid carcinoma. There is keratosis in the depths

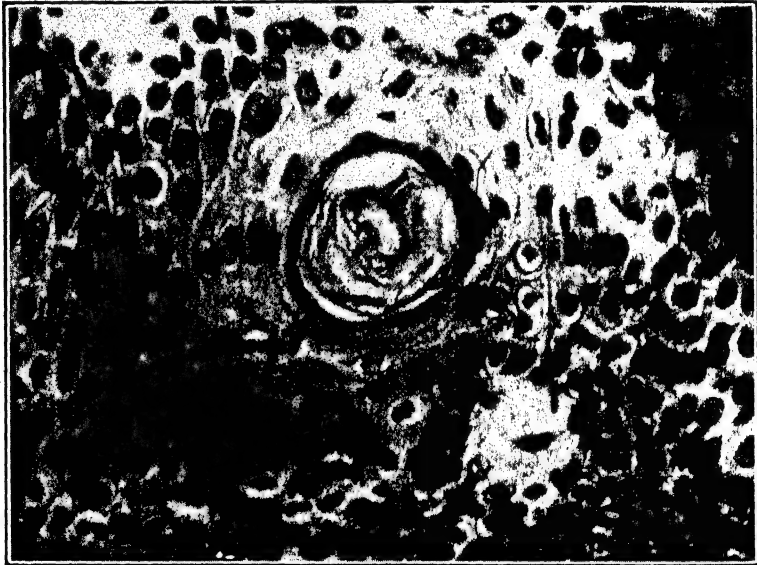


FIG. 541.—Seborrheic keratosis. Keratotic nest or plug next to basal layer.  $\times 475$ .

as well as on the surface. Even under low magnification this feature often enables the correct diagnosis to be made without difficulty. The keratinization of the nests, in which prominent granules of keratin are produced, is preceded by the conversion of the somewhat hybrid-type cells into fully mature squamous prickle cells. (Fig. 541.) The rete tends to be penetrated by dermal papillæ, as a result of which there may be an interlacing of epithelial pegs and dermal papillæ which has been described as "bridging" of the pegs. Melanin pigment may be present in considerable amount in the epithelial cells, accounting for the dark color of the clinical lesion. It must be emphasized that the lesion shows no tendency to a malignant change. The terms senile wart and verruca senilis are unfortunate, because the lesions may occur in young persons, and the name is apt to be confused with senile keratosis. It is better, therefore, to avoid these terms.



**Senile Keratosis.**—In spite of the similarity of name, this is a very different condition from the preceding one. The lesions are small and firm, occurring principally on the face and the backs of the hands of elderly persons, but they may also develop in younger people much exposed to the sun, *e. g.*, farmers and sailors. The condition is a *premalignant* one, with a strong tendency to develop into epidermoid carcinoma. *Microscopically* there is again hyperkeratosis, but the essential change is an irregular and atypical proliferation of the cells of the rete malpighii with hyperchromatic nuclei, loss of cellular polarity, and many mitoses (dyskeratosis). In many cases the picture may suggest a carcinoma in situ. The upper part of the dermis may show a dense infiltration with chronic inflammatory cells and many plasma cells, a state of affairs which should always suggest the possibility of a malignant change in the overlying epidermis.



FIG. 542.—Molluscum contagiosum. The epithelial lobules, the elementary bodies, and cup-shaped expansion of the epidermis can be seen.

**Molluscum Contagiosum.**—This is a contagious condition caused by a virus and characterized by the development of small, white, waxy, almost transparent raised nodules on the skin especially of children. They may last for months or years and then disappear spontaneously. Softening occurs, and a cheesy material can be squeezed out through a small opening in the skin. The stimulation of the virus causes the prickle cells first to proliferate and then to degenerate. As a result of the proliferation the rete pegs project as bulbous swellings down into the corium. (Fig. 542). These swellings, which may be so massive as to be referred to as lobules, compress the dermal papillae into thin septa. The elevated lesion bulges the surrounding epidermis outward so that it comes to assume the shape of a cup. Degeneration of the greatly enlarged prickle cells is accompanied

by the appearance of the really characteristic feature, the *molluscum bodies*. These are rounded eosinophilic hyaline masses which develop in the degenerated cells displacing the nucleus to one side, and represent the elementary bodies of virus disease (Fig. 543). When an emulsion of the elementary bodies is injected into the skin of human volunteers, typical molluscum lesions develop in the course of two or three weeks. The egg-shaped glistening bodies, which can readily be squeezed out of the softened center of the lesion and are sometimes referred to as molluscum bodies, really represent the degenerated cells.



FIG. 543.—Molluscum bodies.  $\times 500$ .

### DISTURBANCES OF PIGMENTATION

The pigment of the skin is melanin produced by the melanoblasts intercalated between the basal layers of cells of the epidermis. The amount of pigment varies in different races. At least in the lower animals and probably in man the melanin granules can move along branching processes of the melanoblasts, so that the pigment passes from the deeper to the superficial layers of the epidermis. The complex problem of melanosis has already been discussed on page 31, so that only brief mention will be made of it here. The pigment is produced by the action of an enzyme, tyrosinase, on a substrate, tyrosin. The melanin can be stained black by

silver stains. The presence of the enzyme can be demonstrated in melanoblasts, either pigmented or non-pigmented, by the dopa reaction.

Melanin is the great protector of the skin against the actinic rays of the sun. It is increased in Addison's disease; it is deficient or absent in *albinism*, a congenital condition in which there is no pigment in the skin, hair, and eyes. *Leucoderma* is a patchy form of albinism, although the term is also used in a different sense. *Vitiligo* is an acquired form of leucoderma. Albinism may occur in the negro. When the negro albino lives in the tropics the situation becomes acutely serious, because such a person is unable to expose his unprotected skin to the fierce sun.

**Xeroderma Pigmentosum.**—This very serious hereditary disease of the skin is characterized by hypersensitivity of the epidermis to ultraviolet light. It usually develops in childhood, sometimes in the first year of life. In the later stages the skin is dry and atrophic with mottled pigmentation so that the lesions resemble those of chronic radiation dermatitis. In addition to the marked destructive changes in the skin there is a pronounced

tendency to the development of basal-cell and epidermoid carcinoma, so that the condition is strongly precancerous. The *microscopic picture* is complex. Hyperkeratosis is associated with marked atrophy of the rete malpighii, although in the later stages there may be patchy acanthosis. Melanin is increased in the basal layers of the epidermis, and numerous melanophores are seen in the superficial layers of the dermis. These layers also show marked destruction both of collagen and elastic fibers. All of these changes, including the tendency to develop carcinoma, may be attributed to an inherited sensitivity to ultraviolet light.

### NONSPECIFIC INFLAMMATIONS: DERMATOSES

This is an indefinite and ill-defined group, and many of the conditions described here might well be considered under other headings. Indeed the term dermatoses merely means skin diseases. A convenient subdivision is into lesions mainly of the epidermis and lesions mainly of the dermis.

The *etiology* of very many of the nonspecific inflammations of the skin is obscure or unknown. In disease elsewhere the investigator has to try to answer the questions how, why and what. Unfortunately in the pathology of the skin he must often content himself with the third of these. The dermatologist must think in different terms from the internist, for he has to deal with the most sensitive organ in the body. *External irritants* must be considered, especially those concerned with occupation, more particularly cleansing agents. Or the irritant may be blood-borne, as in the case of drug dermatitis. *Undue sensitivity to light* may play a part, and photosensitivity may be induced by certain drugs or by circulating porphyrins. Multiplicity of factors must often be considered. Three factors which may act in conjunction or alone are the allergic, the psychogenic and the hormonal. The *allergy* may be to food, drugs, or animal and plant substances, the antigen-antibody reaction taking place in the skin. The *psychogenic factor* often plays a part in skin allergies, just as it does in asthma. It is persons predisposed to emotional conflicts and nervous tension who are likely to suffer from eczema and seborrheic dermatitis. Finally the *hormones*, particularly those of the sex glands and adrenals, exert a profound influence on the skin, hair follicles, and sebaceous glands. The waxing and waning of gonadal function are mirrored in the skin and its pilo-sebaceous system. Thus androgens stimulate surface epithelium and sebaceous glands, tending to produce hyperkeratosis and seborrhea, whereas estrogens have the contrary action.

### Lesions of the Epidermis

**Eczema. Dermatitis.**—These terms signify a nonspecific allergic response of the skin to a wide variety of agents which may act from the outside or through the vessels. The histological picture is correspondingly indefinite. In the acute varieties the lesions are essentially epidermal. Edema, both intercellular and intracellular, result in the formation of vesicles and bullæ either in the rete malpighii or under the stratum

corneum. These contain a few lymphocytes. In the subacute and particularly in the chronic varieties there is often marked acanthosis with elongation of the rete pegs, together with an inflammatory exudate in the corium consisting of a variety of cells, including eosinophils and histiocytes.

**Psoriasis.**—This is a chronic inflammatory disorder marked by the presence of reddish-brown papules and plaques covered with layers of silvery scales. When the scales are scraped away fine bleeding points become apparent which correspond to the apices of the underlying dermal papillæ. The important *microscopic lesions* are in the epidermis. The horny layer is thickened at the expense of the granular layer, and parakeratosis is marked with air spaces between the layers of parakeratotic

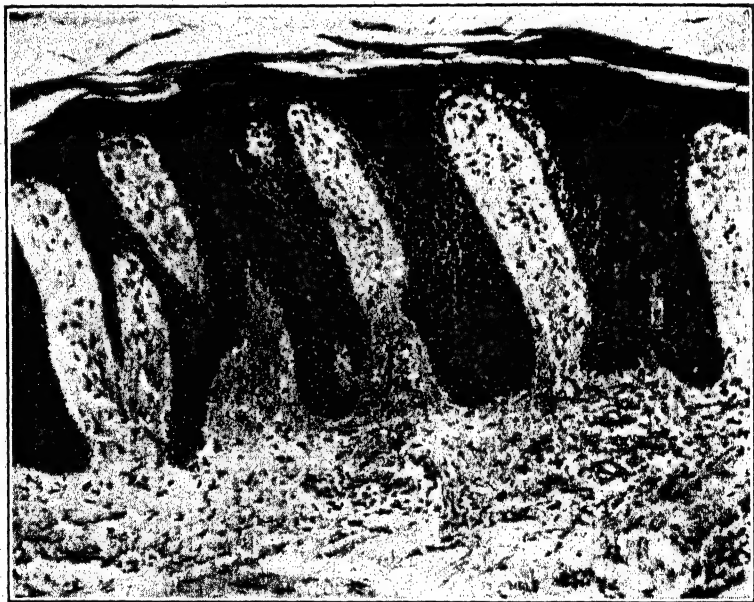


FIG. 544.—Psoriasis. The parakeratotic layer of epidermis is thick and scaly, the dermal papillæ are bulbous and edematous, interdigitating with deep rete pegs, the suprapapillary epidermal plate is thinned, and the corium and papillæ contain a scanty inflammatory exudate.  $\times 125$ .

cells, an arrangement to which the silvery appearance of the scales is due. The rete malpighii overlying the dermal papillæ is extremely thinned, and as these papillæ are elongated and club-shaped with dilated capillaries, it is natural that bleeding should occur when the scales are removed. (Fig. 544.) The rete pegs are also elongated, thin above and thickened below. There is a varying degree of inflammatory exudate in the upper part of the corium, particularly in the papillæ. Polymorphonuclear leucocytes migrate through the epidermis and form micro-abscesses of Monroe in the stratum corneum or just beneath it.

**DERMATITIS HERPETIFORMIS.**—As the name implies, the essential lesions in this disease are vesicular. The vesicles are situated in the deeper layers of the epidermis

and may be subepidermal. There is little intercellular or intracellular edema. The really characteristic feature is the presence of large numbers of eosinophils, both in the vesicles and in the underlying dermis. The blood often shows a marked eosinophilia.

**PEMPHIGUS.**—The characteristic feature of this serious and usually fatal disease is the formation of groups of large bullæ, which may appear at intervals of weeks or months. The bullæ develop deep in the epidermis or in the subepidermal tissue. They contain clear or cloudy fluid and soon rupture. The dermis may or may not show inflammatory changes. It will be seen that it may be difficult or impossible to distinguish between the lesions of pemphigus and dermatitis herpetiformis from microscopic examination. The reason for the fatal outcome is not clear, nor is the cause of the disease known. Possibly it is a virus infection akin to foot-and-mouth disease in animals.

### Lesions of the Dermis

**Urticaria Pigmentosa.**—This peculiar and distinctive disease commonly makes its appearance during the first year of life. At first the lesions may be typically urticarial in type (wheals associated with itching), but later they take the form of pigmented macules scattered over the entire skin. The pathognomonic feature of the *microscopic picture* is the presence of great numbers of *mast cells* in the upper layers of the corium. The specific granules of these cells are not colored by hematoxylin and eosin, but stain intensely with an aniline dye such as toluidin blue. The cells tend to be perivascular in arrangement. Focal collections of mast cells are also found in the spleen, lymph nodes and thymus. The pigmentation is due to the presence of increased amounts of melanin in the deep layers of the epidermis. Subepidermal edema, the characteristic feature of simple urticaria and responsible for the itching, is likely to be present.

**URTICARIA.**—Simple urticaria is characterized by the presence of transient wheals accompanied by itching. The *microscopic* basis of the wheal is edema of the superficial layers of the corium. The collagen fibers, which are swollen and pale, are widely separated by edema fluid, the dermal papillæ are widened and the rete pegs flattened.

**ERYTHEMA MULTIFORME.**—The name implies that erythema is a principal feature, and that the lesions are multiform in character, macules, papules, vesicles and bullæ. It is an acute self-limited disease, more common in young adults, and associated with symptoms suggesting general infection, *e. g.*, fever, sore throat, and enlargement of the spleen and lymph nodes. The principal *microscopic change* is edema of the dermal papillæ, with swelling of the collagen, dilatation of vessels, and marked perivascular infiltration of leucocytes. When vesicles are present there will be edema of the epidermis.

**GRANULOMA ANNULARE.**—This condition is very different from the other dermatoses which have been described so far. It takes the form of small firm nodules arranged usually in a ring-like or annular manner, for the most part on the hands and feet of young persons. The lesions may develop slowly or suddenly, and they may persist for months or years. The *microscopic picture* closely resembles that of the subcutaneous nodules of rheumatic fever and rheumatoid arthritis, except that the lesions are confined to the corium. The center of the nodule presents a picture of necrobiosis or coagulation necrosis rather than the fibrinoid necrosis of rheumatic lesions, and the ghostly outlines of collagen fibers can be traced uninterrupted

through this region (Fig. 545). The central necrotic area is surrounded by palisaded rows of histiocytes and fibroblasts exactly as in the rheumatic nodule. An occasional multinucleated giant cell (not a typical Langhans' cell) may be seen, but, as in the case of the rheumatic nodule, there are no Aschoff cells. The picture must not be mistaken for tuberculosis. There is no true caseation and no true epithelioid cells. The etiology of granuloma annulare is at present unknown.

**NECROBIOSIS LIPOIDICA DIABETICORUM.**—This disease is characterized by lipid deposits in an area of degenerated collagen in the dermis. In spite of the name, diabetes is present in only 80 per cent of the cases. The lesions, usually on the legs, take the form of circular or irregular plaques with a yellow center and violaceous periphery. The *microscopic picture* suggests that of an imperfectly developed granuloma annulare. The degeneration of collagen is not so complete (necrobiosis),

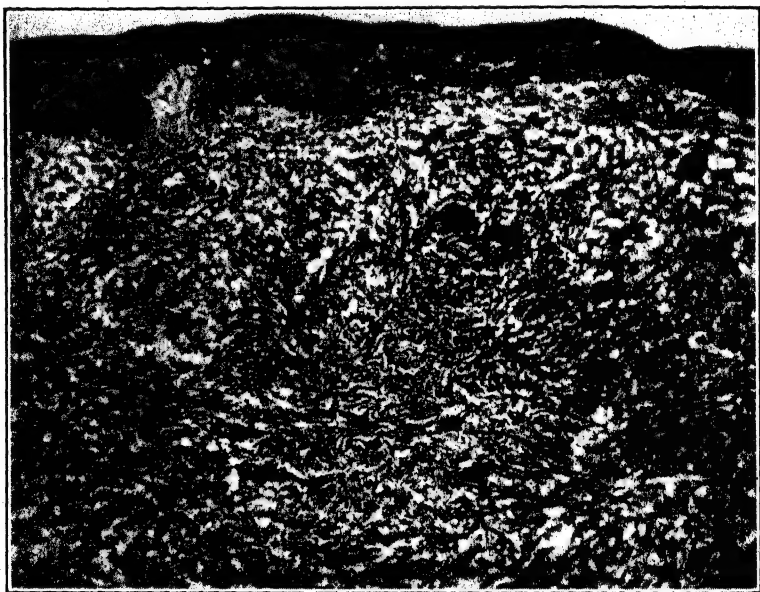


FIG. 545.—Granuloma annulare. Necrobiosis, histiocytes and giant cells in corium.  
× 110

the fibers being swollen, granular and partly fragmented, so that they may extend in various directions. At the periphery of this area there is a chronic inflammatory exudate with epithelioid cells and foreign-body giant cells. Two characteristic features are vascular changes and lipid deposits. The vessels show endarteritis, fibrosis, narrowing of the lumen and occasional thrombosis. These changes account for the degeneration of the collagen. Scarlet red staining of frozen sections reveals numerous granules of lipid between the cells. The changes in the vessels and the lipid deposits serve to differentiate the lesions from those of granuloma annulare.

**Scleroderma.**—Scleroderma may occur in two very different forms, the one circumscribed and benign, the other diffuse and frequently fatal. It is difficult to be certain if these are manifestations of the same disease, but there is no doubt that occasionally the circumscribed may pass into the diffuse form. In *circumscribed* scleroderma (morphea) firm white

patches develop in the skin. These increase in size, but later become stationary and finally disappear, leaving an inconspicuous area of atrophic skin. The *diffuse* form is a very different story. From a local beginning, often on the face and neck, the condition spreads far and wide, until the greater part of the skin becomes hidebound. In the course of time symptoms due to visceral lesions are apt to develop.

The *microscopic lesions* of both forms, whether confined to a few patches in the skin or scattered through the viscera, are similar in essence. It is a disease of collagen and its cement substance. The early lesions are inflammatory in nature, with lymphocytic infiltration and swelling of the collagen fibers which are separated by edema. At a later stage all evidence of inflammation may be absent, the collagen fibers atrophy and become

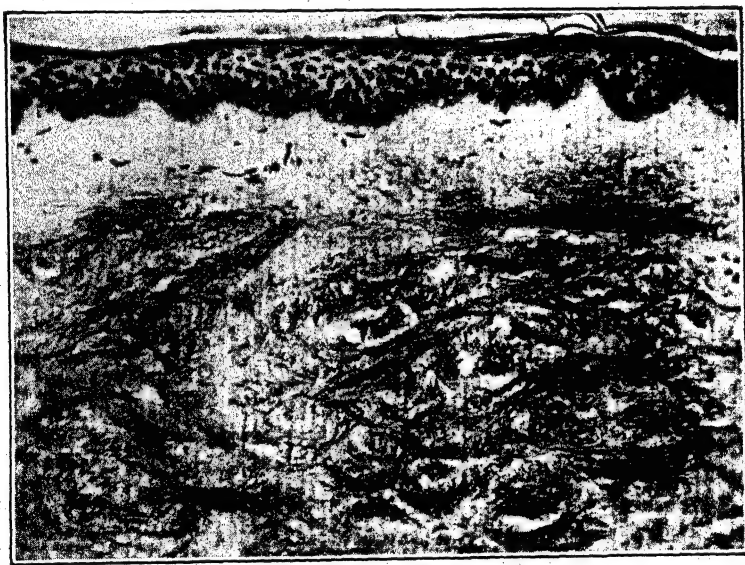


FIG. 546.—Scleroderma. Dense collagen, loss of appendages, atrophy of epidermis and flattening of rete pegs.  $\times 150$

compressed into dense compact masses, the elastic tissue is diminished, the skin appendages disappear except for a few atrophic sweat glands, and the blood vessels of the corium are thickened and their lumen narrowed (Fig. 546). The epidermis tends to be atrophied with flattening of the rete pegs.

Diffuse scleroderma may be regarded as a form, albeit an atypical form, of the group of diffuse collagen diseases. Sclerosing lesions have been described in a great variety of organs, *e. g.*, heart, esophagus, bowel, kidneys, lungs, thyroid gland, and muscles. In all of these locations, in addition to overgrowth of connective tissue, there is degeneration and atrophy of muscle and occlusion of vessels. The disease is, therefore, not strictly a dermatosis, but a progressive systemic sclerosis (Beerman). Calcium deposits (calcinosis) may occur in the degenerated collagen. The cardiac



symptoms may be so marked that the term scleroderma heart disease has been applied. When the lesions are limited to the hands there may be acrocyanosis (*akron*, extremity) resembling that of Raynaud's disease. Esophagitis with chronic ulceration is frequent. Intestinal symptoms may be marked. There may be renal failure with hypertension. Whilst the renal lesions are by no means constant there are usually numerous small infarcts in the cortex, with intimal proliferation in the interlobular arteries and hyalinization of the afferent arterioles and glomerular capillaries (Swarm and Germuth). If the clinical picture resembles malignant hypertension the vessels may show the necrotizing arteritis characteristic of that condition.

**Lupus Erythematosus.**—As in the case of scleroderma this disease may occur in a chronic localized benign form and in an acute disseminated often fatal form, characterized not only by widespread involvement of the skin but also by the presence of numerous visceral and vascular lesions. The latter type, which is one of the diffuse collagen diseases, may develop from the localized form, or the visceral lesions may antedate the cutaneous ones. The characteristic L.E. cell is present in the blood of the discoid as well as the disseminated form, although much less constantly. Disseminated lupus has already been described on page 351.

The *localized* or *discoid* variety consists of small reddish macules usually situated on the nose and cheeks which become confluent and resemble the open wings of a butterfly. It may involve any part of the skin. The lesion enlarges peripherally, with healing and scarring in the center, so as to assume a saucer-like or discoid form. The earliest *microscopic change* is dilatation of the vessels in the upper part of the corium, with extravasation of leucocytes and later lymphocytes and monocytes. Secondary changes in the epidermis are acanthosis alternating with atrophy of the epidermis, keratotic plugging of the hair follicles and sweat ducts, and liquefaction necrosis of the basal-cell layer (Fig. 547). In a lesion on the face of a young woman this picture is characteristic of discoid lupus. In the acute disseminated variety the changes are similar, but the dilatation of vessels and liquefaction of the basal-cell layer are more marked and there is atrophy of the prickle-cell layer. All of these changes are due to the basic lesions in the corium. Exposure to strong sunlight may precipitate a change from the discoid to the disseminated form.

**Lichen Planus.**—In this disease there are characteristic, small, multiple, angular, flat-topped (*planus*) or umbilicated nodules usually limited to the flexor aspects of the wrists and forearms and the legs immediately above the ankles. The *microscopic picture* is also characteristic. In the upper part of the corium there is a sharply limited band-like infiltrate of lymphocytes and other chronic inflammatory cells which hugs the epidermis and may be mistaken for lymphoblastoma (Fig. 548). In addition there is hyperkeratosis, a characteristic increase in the stratum granulosum, acanthosis with elongated pointed rete pegs which have been likened to a saw-tooth, and liquefaction degeneration of the basal cell-layer.

**LICHEN SCLEROSUS ET ATROPHICUS.**—This lesion with the high sounding name consists of flat white papules like those of lichen planus, but with black horny plugs



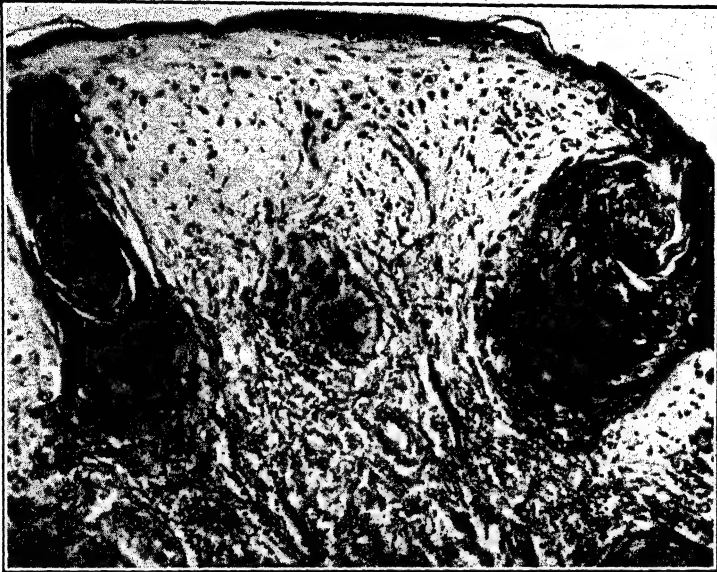


FIG. 547.—Discoid lupus erythematosus. The most striking change is the keratotic plugging of the hair follicles. Other features are colliquative degeneration of the basal layer of cells and atrophy of all layers of the epidermis, smudgy degeneration of collagen in the upper left quadrant, and a cellular infiltrate extending from the superficial to the deep layers of the dermis.  $\times 75$ .

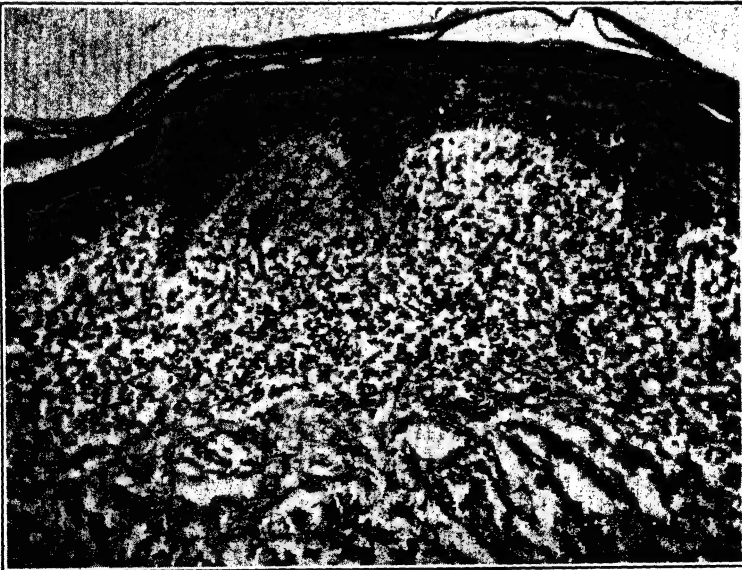


FIG. 548.—Lichen planus. Zone of lymphocytes in dermis, saw-tooth rete pegs, marked granular layer and hyperkeratosis.  $\times 110$

at the openings of the sweat glands and hair follicles, developing later into depressions. *Microscopically* there is marked keratotic plugging of the openings of the ducts and follicles with hyperkeratosis, but atrophy of the rest of the epidermis. The sclerosis is observed in the dermis and resembles that of scleroderma except for the absence of blood vessel changes and the fact that the texture is looser, more edematous, and less homogeneous.

**PANNICULITIS.**—As the name implies, this is not a condition affecting the skin proper, but rather the layer of subcutaneous fibrous and fatty tissue (*pannus*, cloth). A number of forms have been distinguished, but only two will be described. *Nodular, nonsuppurative, relapsing, febrile panniculitis*, known as *Weber-Christian disease*, is marked by development of crops of indurated, tender nodules in the subcutaneous fat. As healing occurs they leave a depression in the skin. *Microscopically* panniculitis may present three stages: the first is the acute inflammatory, the second the macrophagic, and the third the fibroblastic. The first stage, of short duration, is marked by an infiltration of acute inflammatory cells, mainly polymorphonuclear, but without suppuration. In the second stage, which provides the characteristic picture, the cells are mainly phagocytic histiocytes which are invading and engulfing the fat cells. They are, therefore, very swollen with foamy cytoplasm. A few foreign-body giant cells may be present. In the third stage fibroblasts replace the macrophages, collagen is laid down, and fibrous tissue formed. Neither the corium nor epidermis are involved. The etiology is unknown.

*Erythema induratum* (*Bazin's disease*) is a form of panniculitis in which indurated bluish-red nodules develop usually in the calves of the legs. As a rule they are associated with tuberculous lesions in other organs, but the relation to tuberculosis is rather indefinite. The *microscopic picture* is tuberculoid rather than characteristically tuberculous, and caseation is often absent. There is fat necrosis associated with a nonspecific chronic inflammatory reaction.

## SPECIFIC INFLAMMATIONS

Inflammation of the skin may be caused by bacteria (tuberculosis, syphilis, etc.), fungi (blastomycosis, etc.), viruses (smallpox, etc.), and animal parasites (scabies, etc.). These have already been described in the section on General Pathology, but impetigo may be considered here.

**IMPETIGO CONTAGIOSA.**—This contagious disease caused by pyogenic cocci, both staphylococci and streptococci, is a good example of inflammation confined to the epidermis. Exposed parts such as the face and hands are affected, often as the result of scratching. The bacteria penetrate the horny layer from without. First a vesicle and then a pustule develops between the stratum corneum and rete malpighii, polymorphonuclears wandering through the epidermis from the vessels of the corium. Inter cellular edema may be marked in the rete, and the pus cells are readily seen. When the pustule ruptures it is covered with a crust of fibrin.

## TUMORS OF THE SKIN

As the skin is of such complex structure it is natural that a wide variety of tumors should arise from it. Thus there may be tumors of epidermal and mesodermal origin, tumors of the skin appendages, pigment cells, nerves, vessels, muscles, and lymphoid tissue. Some of these tumors have already been described in the section on tumors in Chapter 10, because they are neoplasms which are not confined to the skin. Others which are

primarily tumors of the skin will be considered here. There is bound to be some overlapping with regard to the hypertrophies and neoplasms. Thus some writers will include verruca senilis (seborrheic keratosis) with the former and others with the latter group.

### Epidermal Tumors

**Epidermoid Carcinoma.**—This type of tumor may arise from squamous-cell epithelium wherever it occurs. It may also originate from columnar epithelium, especially when that epithelium has undergone squamous metaplasia as in the bronchus. It has already been considered on page 267.

It may be noted here that spontaneous healing of multiple squamous-cell carcinoma may occur in rare instances (Currie and Smith). In one such case the condition was present for twenty-one years. These tumors are widely distributed on the face, ears and limbs, and develop into malignant ulcers which heal spontaneously. There is often a familial history. At least some of the tumors appear to arise from hair follicles, and it has been suggested that the sebaceous glands may secrete a weak carcinogen derived from fatty-acid breakdown products of their secretion.

**Basal-cell Carcinoma.**—*Rodent Ulcer.*—This is a variety of squamous-cell carcinoma which differs both clinically and pathologically from typical epidermoid cancer. It is relatively benign, of remarkably slow growth, and does not involve the regional lymph nodes. It presents the anomaly of a tumor which is relatively undifferentiated and is yet of low malignancy. Being undifferentiated it responds well to radiation, but not if it has infiltrated the underlying bone. The distribution is highly characteristic. The lesion occurs on the upper part of the face about the cheek, nose, and ear, above a line drawn between the tip of the ear and the angle of the mouth. It is, however, by no means confined to this region, and may occasionally occur on other parts of the skin. Not infrequently rodent ulcers are multiple, the skin of an area (usually the face) developing a tumor-forming tendency (Fig. 125, page 226). Exposure to bright sunlight appears to be a causal factor. In Australia where the light is very strong and the humidity very low the disease is extremely common. As many as 50 cases a day may be seen in the out-patient department at Sydney. The conditions in Australia are peculiar, for it is a country with a tropical sun in which there is nothing but white labor. In other tropical countries those who are continually exposed to the brilliant glare have colored (protected) skins. It is interesting to note that the large Italian element in the labor population in Australia is relatively immune. The disease is much commoner at the north end of New Zealand than in the south. The tumor slowly erodes the deeper tissues, and in this way may cause great destruction of the nose, the contents of the orbit, etc. For this reason it is commonly called *rodent ulcer*.

The *microscopic appearance* is quite different from that of epidermoid carcinoma. It consists of solid masses of darkly-stained cells which extend down into the dermis (Fig. 549), although often no connection with the epidermis may be seen in a given section. The columns extend down

to a uniform level, and their ends have an expanded club-shaped appearance. This gives a geographic arrangement of capes, bays and promontories. There is none of the eosin-staining so characteristic of epidermoid carcinoma, no cell nests, no cornification. There are usually no mitotic figures, but they may occur in the more rapidly-growing forms. Melanin pigment may be so abundant as to be misleading. Occasional variations in this uniform picture may occur. Thus the structure may become lacy, cysts may form due to edema and liquefaction of the stroma, whilst in the rare *basosquamous type* there are nests of squamous cells like epithelial pearls.



FIG. 549.—Basal-cell carcinoma (rodent ulcer). The basal-cell character of the growth is evident.  $\times 90$ .

The *origin* of the tumor has been a matter of dispute. The term basal-cell carcinoma indicates the belief that the origin is from the basal-cell layer of the epidermis. It seems probable that many of these tumors arise from the hair follicles or their anlage. Wallace and Halpert, indeed, have suggested the name *trichoma*. It is of interest to recall that while most of the malignant epithelial growths of the skin mimic the pattern of the epidermis, practically all the benign growths mimic the pattern of the skin appendages. This is true of the so-called basal-cell carcinoma.

**PAGET'S DISEASE.**—This condition has already been described on page 685 in connection with carcinoma of the breast. It is mentioned here because in some cases

the disease seems to begin in the skin as an *intraepidermal carcinoma* with later involvement of the ductal epithelium.

**BOWEN'S DISEASE.**—This also is an intraepidermal carcinoma rarely developing into an invasive squamous-cell carcinoma. It is an example of preinvasive carcinoma (see below). There is acanthosis with elongation of the rete pegs, but the basal layer is intact. The characteristic feature is the atypical character of the epithelial cells, many of which show marked vacuolization with a cytoplasmic halo surrounding the nucleus, an appearance similar to that of Paget cells. The scaly patches occur on the trunk and the extremities.

**PREINVASIVE CARCINOMA.**—This condition, also called *intraepithelial carcinoma* and *carcinoma in situ*, may be observed in a number of locations, such as the stomach and bronchus, but to the pathologist concerned with the diagnosis of biopsy specimens the sites of paramount importance are the cervix and the skin. In order to

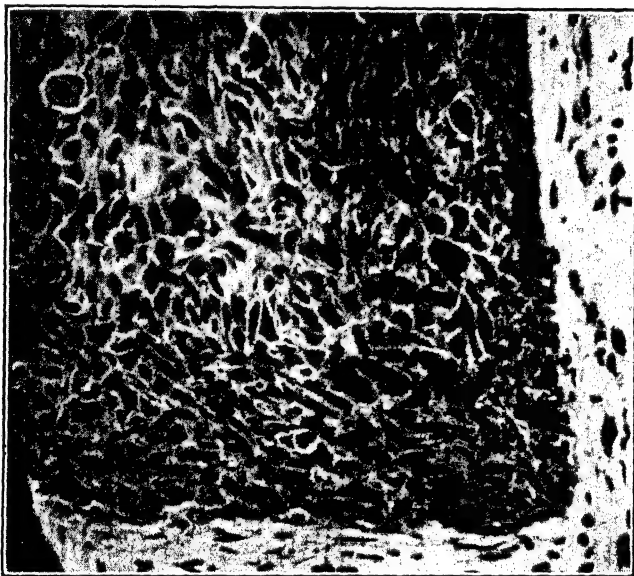


FIG. 550.—Preinvasive carcinoma. Dyskeratosis as evidenced by disorderly arrangement of cells (loss of polarity), variation in size and chromatic character of nuclei, and mitoses.  $\times 250$

justify this diagnosis the various layers of the epidermis should show evidence of dyskeratosis, *i. e.* cellular unrest and malignant transformation such as acanthosis, hyperchromatism, loss of cell polarity (jumbling of cellular arrangement) and increased number of mitoses (Fig. 550). When only the basal layers are involved the condition should be regarded merely as basal-cell hyperplasia. There is no invasion of the dermis, nor is there any guarantee that this will occur, but the picture must arouse apprehension. More particularly is this the case when marked lymphocytic infiltration of the underlying dermis suggests the action of some agent released from the proliferating cells of the epidermis.

**PRECANCEROUS LESIONS.**—It is in the epidermis that the lesions known by the somewhat ambiguous name of precancerous can most readily be observed. Although all writers do not agree with this statement, a precancerous lesion should be distinguished from carcinoma *in situ* or intraepithelial carcinoma. The former

is not yet cancer, whereas the latter lesion, in the opinion of the pathologist, is a definite cancer although not yet invasive. Paget's disease of the skin and Bowen's disease are examples of carcinoma in situ. Senile keratosis, as well as leukoplakia, kraurosis vulvæ and radiation dermatitis which present the same histological picture, xeroderma pigmentosa and junctional nevus are all examples of true precancerous lesions. They are in no sense malignant, but they have a tendency to develop into cancer and must alarm the clinician for that reason.

### Tumors of the Appendages

**Sweat Gland Tumors.**—The nomenclature of tumors of the sweat glands is extremely complex and confusing because of the varied microscopic picture. Their names are legion, and each writer seems to delight in inventing new ones. For a detailed consideration of the subject the reader must consult works on skin pathology, although Gates, Warren and Warvi in their full review of the subject rather discourage this by remarking that "the literature is confusing and largely casuistic." Three common terms with their derivations may be mentioned. These are spiradenoma (*speira*, a coil), syringoma (*syrinx*, a tube), and hidradenoma (*idros*, sweat).

The tumors are adenomas which are usually solid but may be cystic. Rarely carcinoma may develop, but this is of low malignancy and only locally invasive.

*Spiradenoma* or *hidradenoma*, the commonest of the tumors, also known as cylindroma, an ambiguous and confusing term, is a disease, often hereditary, characterized by multiple tumors of the skin. When these occur on the scalp they may cover the head like a wig or turban, so that the lesion is known as a *turban tumor*. The *microscopic picture* is one of sharply limited cell masses and strands in which are embedded alveolar spaces lined by cuboidal epithelium, each mass being surrounded by a hyaline membrane. The cells in the center have large pale nuclei and represent the secreting type; they are surrounded by a palisade of cells with small dark nuclei, which appear to be myoepithelial in nature. These tumors must not be mistaken for basal cell carcinoma, in which the pattern of growth is quite different.

*Papillary Syringocystadenoma*, as its name implies, arises from the duct of the gland. The duct is dilated, and the resulting cyst contains numerous villus-like projections covered by a double layer of cells, the outer layer being myoepithelial and the inner layer secreting cells (Fig. 551).

The *papillary hidradenoma* is an adenoma of apocrine glands occurring almost exclusively on the labia majora and perineum of women. Into a cyst-like lumen project numerous papillary processes covered by a single layer of cylindrical, eosinophilic, secreting cells like those of an apocrine gland. The picture resembles that of cystic lobular hyperplasia of the breast.

**SEBACEOUS GLAND TUMORS.**—This group is as simple as the sweat gland group is complex, for the only one which deserves mention is *sebaceous adenoma*. The lesion is more a hyperplasia of the glands than a true tumor. It occurs as small yellow papules chiefly on the nose, cheeks and forehead. The microscopic picture is simple overgrowth of the sebaceous glands. Tuberous sclerosis of the cerebral cortex may be associated with multiple sebaceous adenomas. In rare cases locally infiltrating carcinoma has been described.

**TUMORS OF HAIR FOLLICLES.**—*Adenoid cystic epithelioma*, also known as *trichoeptithelioma* and *Brooke's tumor*, is believed to arise from the hair follicles. It

forms multiple smooth tumors on the face and chest, occurs at a much earlier age than basal cell carcinoma for which it may be mistaken, and forms a heaped-up lesion on the surface. The lesion consists of solid masses of dark cells like those of a basal-cell carcinoma and cystic spaces lined by squamous stratified epithelium

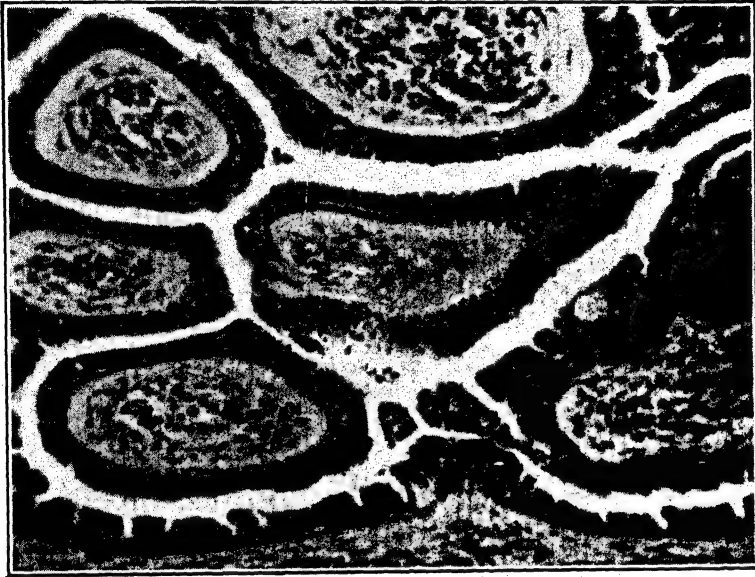


FIG. 551.—Sweat gland tumor. This is a papillary syringocystadenoma with papillary processes in a dilated duct. The double layer of cells lining the cyst can be distinguished.  $\times 200$ .

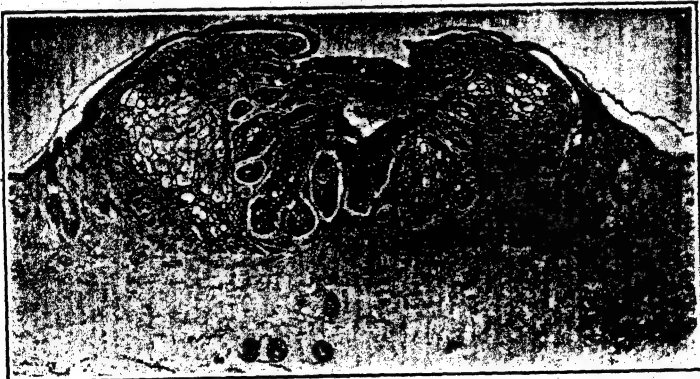


FIG. 552.—Adenoid cystic epithelioma showing cystic spaces. Note the resemblance to rodent ulcer.  $\times 14$ .

and filled with keratin (Fig. 552). The tumor is quite benign and does not infiltrate the surrounding tissue.

*Basal-cell carcinoma* is believed by some to arise from the cells of the hair follicle. This matter has already been discussed on page 960.



### Pigment Cell Tumors

**Nevus.**—A nevus is a mole. It is usually pigmented, but may not be; the color varies from gray to brown or jet black. A pigmented nevus must be distinguished from other pigmented lesions of the skin such as pigment spots, seborrheic keratosis, and dermatofibroma in which there is an increase of melanin on the surface and hemosiderin in the deeper parts. A microscopic distinction of importance is drawn between the intra-dermal nevus (the common mole) and the junctional nevus (see below). The former remains benign and the latter may become malignant. In the gross a distinction can also be drawn. The intradermal nevus is raised and hairy, whilst the junctional nevus is flat and may give the appearance of a drop of brown paint with a spreading margin, especially when it is becoming malignant. The nevus varies greatly in size, being usually quite small, but sometimes covering a large area of the body.

Nevi are so common that nearly everyone has at least one tiny one, and the average person has over 20 pigmented moles. They are usually situated on the face, neck or back, but they may occur anywhere. Rarely a nevus occurs in the pigmented part of the eye. A nevus is a congenital condition, but it may not be apparent at birth, and many pigmented moles do not appear until adult life. It seems probable that the lesions are under the influence of and may be activated by steroid hormones. The great majority of nevi pursue an uneventful course. They may grow slowly for a time, remain quiescent for a long period, and gradually atrophy. The beginning of a *malignant change* may be indicated by the presence of a pink halo caused by the inflammatory reaction which accompanies such a change, increase of size and pigmentation, and itching. The dangerous sites are the palm, the sole, the digits (especially in the region of the nails), the genitals, the anus, and places exposed to continued trauma. The transformation is often slow and insidious, for melanoma enters by stealth like a thief in the night, but any sudden increase in the rate of growth should at once arouse a suspicion of malignancy.

**HISTOGENESIS.**—The mode of origin of the nevus has been and still is a matter of endless debate. The older views, having been discarded, may be passed by. At the present time two theories hold the field, the epidermal (epithelial) and the neurogenic. For the arguments in support of the former the reader is referred to the article by Allen, for those in support of the latter to the papers by Masson. The controversy revolves around two points: (1) the nature of the melanoblasts, (2) the question as to whether additional structures are involved in the production of the nevus.

Even a cursory examination of a few surgical sections will suggest the possibility that the groups of nevus cells in the dermis represent downgrowths from the epidermis which have become cut off and isolated. The champions of the epidermal school hold that melanoblasts are merely epithelial cells which possess the power of forming pigment, that these proliferate in the basal layer of the epidermis and penetrate into the underlying dermis, where they may become cut off from their source of origin. The process may be arrested at any stage, but in each case the resulting lesion is a nevus.

The epidermal theory is so simple and satisfactory that, by comparison, the neurogenic theory appears complex and far-fetched, if not fantastic. But the body



itself is complex and many features of even normal development (*e. g.*, the eye) appear to be fantastic. The basic fact to be faced is that some structures and arrangements only become apparent with perfect fixation, trichrome stains and silver impregnation of cytoplasm. Anyone who has seen a demonstration by Pierre Masson of Montreal illustrated by color photomicrographs of breath-taking perfection has a new world of structure revealed to him which is invisible with hematoxylin and eosin staining, and which cannot be reproduced with complete satisfaction in black and white illustrations.

In brief outline Masson's views are as follows. A fully developed nevus is a cutaneous malformation in which the two principal components are melanoblasts and the nerves of the dermis. The former come from above, the latter from below.

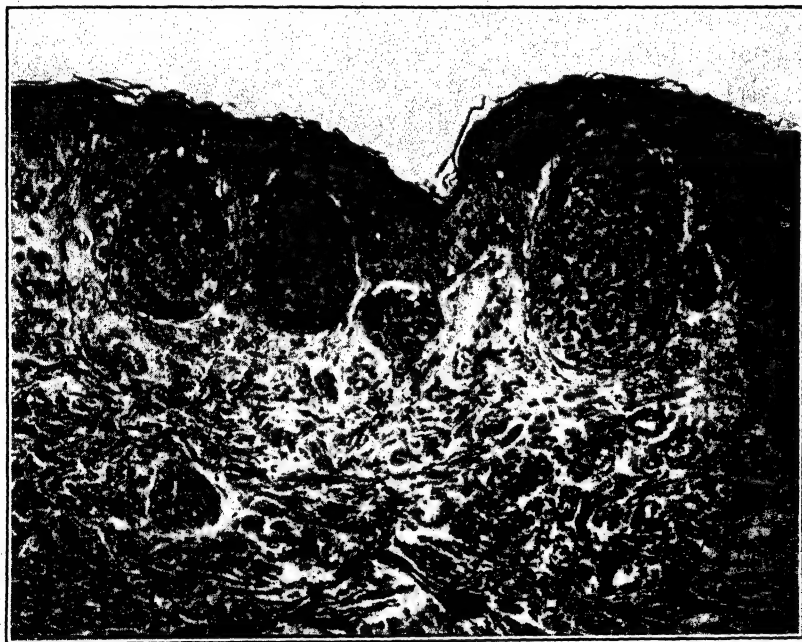


FIG. 553.—Intradermal neuro-nevus. The process of Abtropfung has been completed. In the dermis there is a proliferation of cells of nervous origin. (Kindness of Professor Pierre Masson.)

Melanoblasts are cells resembling monocytes which occur in the basal layer of the epidermis. They are dopa-positive by reason of the melanogenase they contain, and may be pigmented or non-pigmented. (For discussion of the dopa reaction see page 32.) The pigment is rendered prominent by Fontana silver staining. Melanoblasts transfer their pigment to adjoining epidermal cells and to dermal macrophages that become melanophores or pigment carriers, which are dopa-negative but Fontana-positive. The melanoblasts gradually lose their melanin and enzyme and are carried to the surface. They are replaced by young cells.

In the nevi of infants there is overproduction of melanoblasts and melanin. The melanoblasts may separate the malpighian cells from the basement membrane. There is marked excretion of melanin into the underlying dermis, where it is taken up by melanophores. Thus is formed the *junctional nevus*, (epidermal or marginal

nevus), which is the characteristic nevus of childhood. Or there may be a dropping down of cells, an *Abtropfung* as it was called by Unna, in which groups of melanoblasts penetrate the basement membrane, at first hanging like drops from a roof, then becoming detached and falling down into the dermis, a new basement membrane forming above the cell clusters (Fig. 553). Some of the melanoblasts arise from such derivatives of the epidermis as the hair follicles and the sebaceous and sweat glands. As long as the migration of melanoblasts goes on the lesion is known as a *compound nevus*. When the *Abtropfung* has ceased and all connection with the epidermis has disappeared the lesion becomes an *intradermal nevus* (dermal nevus). This is the common nevus or mole of adult life. So far the process is identical with that described by the epidermal school.

There now occurs a multiplication of the cells of the sheath of Schwann in the cutaneous nerves. The schwannian cells break through the membrane which surrounds them and invade the connective tissue. They form a layer of cells separated from the melanoblasts by a zone of normal tissue. The melanoblasts seem to exert an attraction on the schwannian cells, for the former grow down and the latter grow up, till they meet in the dermis and merge together. The nevus tissue, which is derived from two distinct sources, now becomes a single structure, a *neuro-nevus* (Fig. 553).

The natural history of the nevus demands attention. From the age of three or earlier changes begin which transform the juvenile into the adult nevus. These changes are most marked shortly before puberty. At a very early stage there is a gradual depigmentation of the melanoblasts. At puberty and in the adult only those cells in the superficial region of the papillary dermis are pigmented and dopa-positive. The pigment has been taken up by the dopa-negative melanophores. The depigmented melanoblasts cannot be distinguished from the schwann cells. The cells of the lesion are now of two varieties. Near the epidermis they are round or polygonal, whilst deeper they are more elongated and arranged in anastomosing fascicles. These two types may be called the epithelioid and the fasciculated; one or other type may predominate.

Masson remarks that the nevus shows the cytological and histiogenetic properties that are specific for schwannian tissue. These are not apparent in thin sections stained with hematoxylin and eosin, they are more readily seen in trichrome stained material, and are most obvious in thick sections impregnated with silver nitrate for the demonstration of cytoplasm.

In the development of peripheral nerves a multinucleated syncytial tube of schwannian cells is formed which undergoes longitudinal partitioning. In the Meissner tactile corpuscles there is a further separation of the syncytium into a pile of superimposed discs or leaflike foliated laminæ (*lâmes foliacées*), through which the tactile neurites (axis cylinders) wander and end. The nevus, when properly fixed and stained, presents the same characters. The nevus tissue is traversed by neurites coming from nerves whose schwannian syncytium furnishes the neuroid elements of the lesion. After the amalgamation of the two elements the cells lose their separate identity and form a continuous syncytium, an arrangement profoundly different from that of such tumors as carcinoma or lymphosarcoma.

The nevus corpuscles and foliated laminæ resemble those of Meissner's corpuscles. It is a common mistake, an error committed in previous editions of this book, to say that the supporters of the neurogenic theory believe that the nevus arises from Meissner's corpuscles. Tactile corpuscles are confined to the palmar and plantar regions, more particularly in the fingers and toes. Compound nevi, on the other hand, develop everywhere except in these regions, where the nevus is always of the junctional type. In the rare cases where *Abtropfung* does occur there is no accompanying schwannian proliferation. It would appear as if in the fingers and toes the schwannian force is exhausted by the formation of Meissner's

corpuscles. All nevi are neuro-nevi except in the palmar and plantar regions.

It may be mentioned that in a more recent communication (1952) Berkheiser and Rappoport support the view of Masson regarding the dual origin of nevi from intraepidermal melanoblasts and proliferated schwannian cells.

*Malignant change* when it does occur is most likely to affect the junctional nevus after puberty. It is exceptional in the intradermal form. It would appear that the neurooid element has an inhibitory effect on the tendency to malignancy.

#### MICROSCOPIC APPEARANCE.—

From the discussion on pathogenesis it is evident that the histological picture will depend on whether the nevus is intradermal, junctional or compound.

The *intradermal nevus* is the common form in the adult. It represents the completed stage of development, and is correspondingly quiescent. Nests and cords of closely packed "nevus cells" occupy the superficial layers of the dermis and sometimes the dermal papillæ (Fig. 554). The cells in superficial lesions are large, pale and polyhedral, but in the deeper lesions they are more fusiform and it is here that connections with nerve structures may be detected. The nests and sheets of cells are circumscribed, but at their lower limit they tend to trail off in an undecided manner which must not be mistaken for malignant invasion. The amount of melanin varies greatly. The pigment is



FIG. 554.—Intradermal nevus. The nevus cells are in the dermis and have no connection with the epidermis.  $\times 100$ .

contained in dopa-positive melanoblasts and in more peripheral fusiform dopa-negative melanophores. The overlying epidermis is not involved in the process, but may be either unduly papillary or flat.

The *junctional nevus* (epidermal nevus, marginal nevus) presents a highly distinctive appearance (Fig. 555). In the deeper layers of the rete, often in the rete pegs, there are sharply circumscribed collections of large loosely arranged cells (melanoblasts), some of which are sprinkled with melanin granules. The corium is not involved. The lesions may be limited to one spot or there may be alternating nevoid and normal portions of epidermis over an area of some size. The importance of the junctional nevus lies in the fact that it is this variety which is liable to develop into

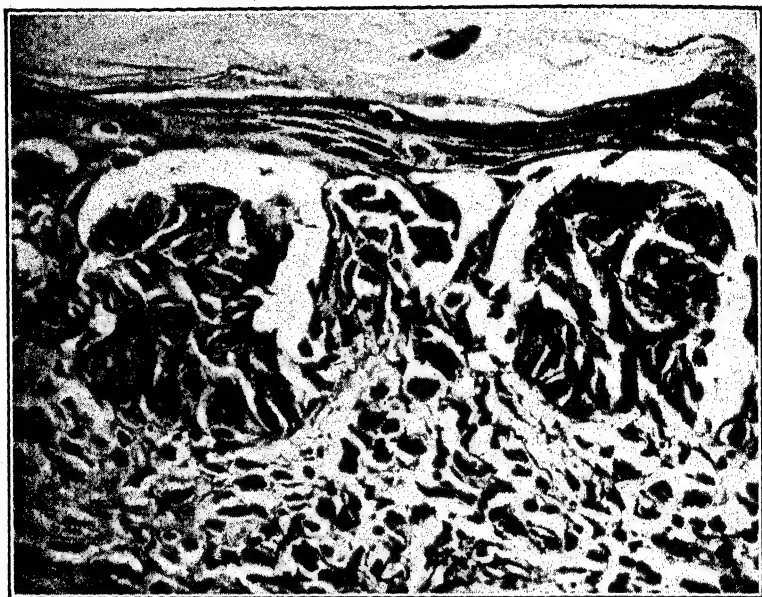


FIG. 555.—Junctional nevus. The melanoblasts, which were filled with melanin granules in the original section, are confined to the deeper layers of the epidermis. The smaller cells in the underlying dermis are inflammatory in nature.  $\times 375$ .



FIG. 556.—Compound nevus of combined junctional and intradermal type. The junctional changes in the epidermis are marked. There is direct continuity between the nevus cells in the epidermis and dermis.  $\times 150$ .

malignant melanoma after puberty. The presence of alternating or "skip" lesions may explain apparent recurrence of the melanoma after surgical removal (Allen and Spitz). This may not be a true recurrence but rather activation of outlying junctional nevi.

The *compound nevus* is a combination of the junctional and intradermal forms (Fig. 556). Nearly all intradermal nevi before puberty show this combination. In the adult it is very much less frequent, and it is these cases which hold the threat of possible malignancy.

**BLUE NEVUS.**—This is in an entirely different class from the other members of the group. It is the blackest of pigmented lesions and the most benign, in general less than 1 cm. in diameter, occurring in childhood and persisting unchanged throughout life. The usual sites are the face, the back of the hands and feet, and the soles.



FIG. 557.—Blue nevus. Fibroblastic proliferation with deeply situated pigment cells. The epidermis is unaffected.  $\times 175$ .

The *Mongolian spot* is a rather larger lesion at the lower end of the spine. The color fades about the third or fourth year of life. Both of these rare lesions consist of interlacing fasciculi of spindle cells amongst which are interspersed pigmented cells. Some of these are melanoblasts, dopa-positive and containing fine granules of melanin. They are situated in the deeper region of the skin, and are surrounded by heavily pigmented melanophores (Fig. 557). On account of the type of cells, their position and the presence of pigment, the lesion may be mistaken microscopically for a dermatofibroma containing hemosiderin granules. The differentiation can readily be made by means of the Prussian blue reaction for iron. The blue nevus hardly ever becomes malignant, nor are there any changes in the overlying epidermis.

**Malignant Melanoma.**—This highly malignant tumor is usually referred to merely as melanoma. It arises from melanoblasts in a nevus of the skin (Plate XXXII) or in the pigmented coat of the eye. On the palms, soles and genitalia

no preëxisting nevus may be evident clinically, but the possibility of a junctional nevus cannot be excluded. In rare instances a melanoma may originate in other locations such as the mucous membrane of the rectum or nose or the meninges. It seems probable that malignant melanomas are under the influence of steroid hormones. Nevi only become malignant after puberty, and pregnancy has a bad influence on the course of the tumor. On the other hand the prognosis after surgical removal is a good deal worse in men than in women, especially in lesions of the head and neck (Allen and Spitz). The incidence is about the same in the two sexes. It may be noted that pigmented tumors are common in white and gray

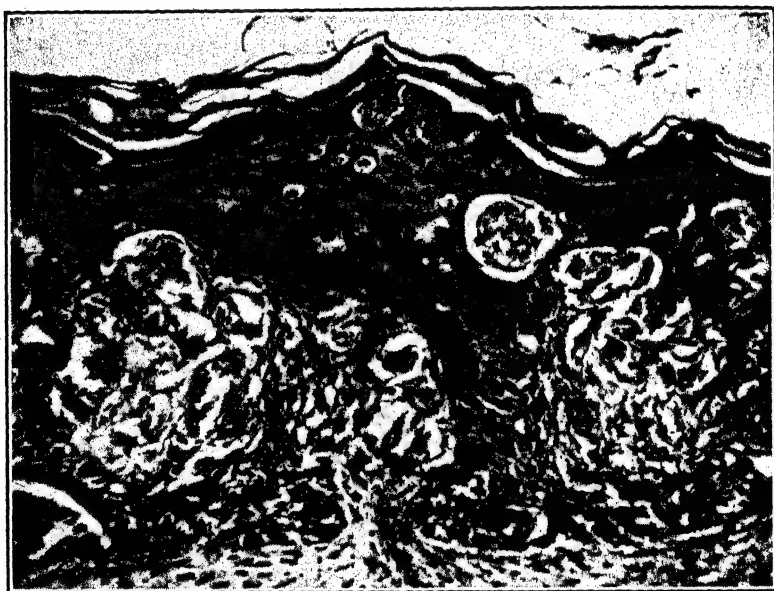


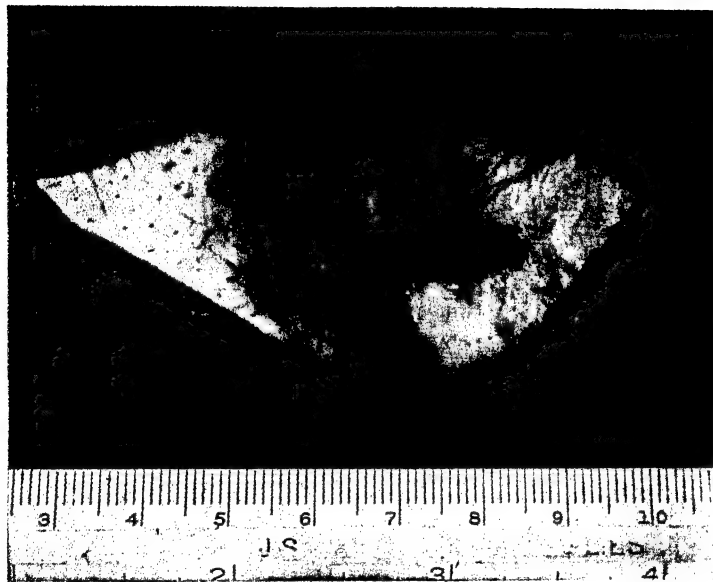
FIG. 558.—Junctional nevus showing malignant transformation. The junctional change involves all layers of the epidermis, the nevus cells are loosened, and some are surrounded by a clear halo.  $\times 175$ .

horses but quite rare in dark horses. It is said that if a white horse lives long enough it is almost certain to die of melanoma. It has also been said that a farmer could paint his fences with the pigment from the metastatic melanomata in a white horse, but I cannot vouch for this statement; it might depend on the length of the fences.

In the secondary growths the tumor cells continue to form pigment in enormous quantities. As much as 300 grams of melanin have been extracted from a liver filled with metastases. In rapidly growing tumors the pigment may escape into the blood (melanemia) and be excreted in the urine (melanuria). In rare cases there is a diffuse staining of the lining cells of the blood vessels and serous membranes.

**MICROSCOPIC STRUCTURE.**—The melanoma of the skin develops from the junctional type of nevus, although it would be unwise to say that this is

## PLATE XXXII



*Junctional Nevus and Melanoma.*

The nevus presents an appearance of two drops of dark oil in the skin. The large red mass is the melanoma, which microscopically was almost lacking in pigment, the surface being inflamed and ulcerated.

invariably the case. Both the nuclei and cytoplasm of the nevus cells show suggestive changes. The proportion of nucleus to cytoplasm is increased, the nucleolus is enlarged, hyperchromatism is present, and mitoses may be observed. The cytoplasm is often vacuolated and sprinkled with fine melanin granules, and the cells become loosened and may be surrounded by a clear halo so as to have a resemblance to Paget cells. These changes extend throughout the epidermis as far as the stratum corneum, a highly suggestive appearance. (Fig. 558.) Epidermal hyperplasia is nearly always present and must not be mistaken for squamous cell carcinoma.

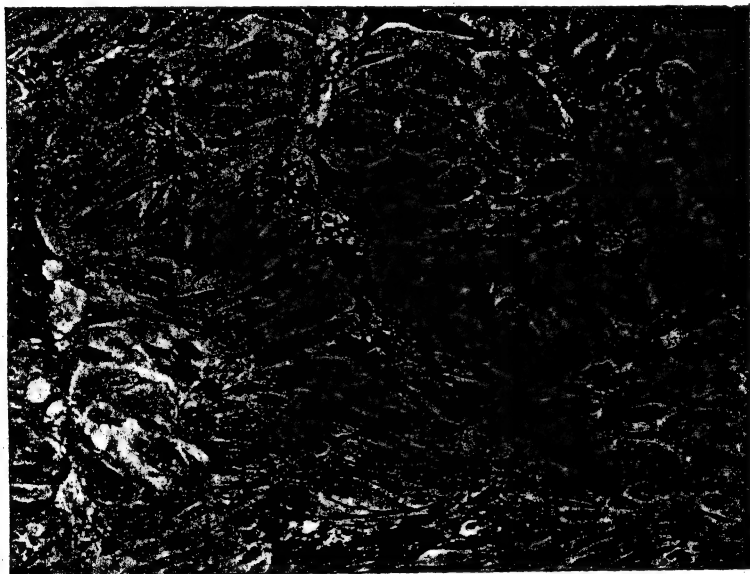


FIG. 559.—Malignant melanoma in skin showing characteristic acinar grouping of the cells.  $\times 275$ . (Boyd's Surgical Pathology, courtesy of W. B. Saunders Co.)

Invasion of the dermis is indicated by the presence of circular or polyhedral cells with abundant spongy cytoplasm and fine pigment granules. The tumor cells may form small clusters in the subepidermal lymphatics, a grim indication of the early stage at which lymphatic dissemination of the tumor may occur. A subepidermal zone of inflammatory cells, mostly lymphocytes, is always suggestive of a malignant change. In the fully developed melanoma the large tumor cells in the dermis often show an alveolar arrangement, the groups being separated by a fine stroma (Fig. 559), but no tumor presents a more varied histological picture, and it may simulate a squamous or basal cell carcinoma, an adenocarcinoma, and, if the cells become fusiform, a fibrosarcoma. Pigmentation is usually marked, but this feature is very variable, and in one part of the tumor the cells may be loaded with melanin, whilst in another part they contain none. The melanoblasts may liberate their pigment, which is then taken up by phagocytic melanophores.



**SPREAD.**—A melanoma is important not because of any local disturbance it produces, for usually it remains small; it kills by producing widespread metastases. The tumor cells spread by the lymphatics to the regional lymph nodes and by the blood stream to distant parts, although in melanoma of the eye there is no lymph spread. The tumor spreads mainly and at first exclusively by the lymphatics; the regional lymph nodes soon become enlarged. Blood spread is a late event, and may be absent nearly until the end. When it does occur it is usually very wide, so that hardly an organ may escape. The skin is a common site of metastases. Secondary growths appear early in the skin; multiple growths of the skin even though non-pigmented should suggest a search for a primary melanoma. A history of loss of an eye from disease and an enlarged liver should suggest an ocular melanoma.

*Melanoma in childhood* must be differentiated from adult melanoma (Spitz). The two are similar microscopically, with the exception of the fact that in about half the juvenile cases giant cells are present. But there is a world of difference in their clinical behaviour. The juvenile melanomas, in spite of their apparent malignancy, remain localized in the majority of cases. With the arrival of puberty this difference disappears, and the tumors show the same tendency to metastasize as in the adult. It would appear that some inhibitory factor exists before puberty which prevents the spread of the tumor. It is natural to suggest that such an influence is hormonal in character.

### Tumors of the Dermis

Many tissues and cells mingle in the dermis. There is fibrous tissue, blood and lymph vessels, nerves, plain muscle and lymphoid tissue. Fibromas and fibrosarcomas, hemangiomas and lymphangiomas, neuromas and neurofibromas, leiomyomas and lymphoblastomas are described elsewhere in this book. A few special types of tumor will be considered here.

**Dermatofibroma.**—In spite of its name, this common lesion is not a true fibroma of the skin. It is a small, hard, non-encapsulated lesion of the corium, usually occurring on the extremities. It is composed of large, irregular, fusiform cells running in many directions and interlacing. It may be highly cellular, or may have abundant collagen and few cells. An important feature is the ill-defined margin with infiltration of the surrounding tissue, and the cellular forms are easily mistaken for melanoma and neurofibroma. Phagocytic histiocytes often contain hemosiderin and lipids. The Prussian blue reaction for iron will readily distinguish the pigment from melanin. The histological features are well shown in Stecker and Robinson's paper, which reports 60 cases from my department in Toronto.

It seems probable that dermatofibroma is in essence the same as the condition known as *sclerosing hemangioma*. The capillaries of the angioma become obliterated, whilst segregated groups of endothelial cells remain. Accumulations of lipid and hemosiderin resemble those of dermatofibroma. They are probably extracted from the circulating blood (Gross and Wolbach), although to a lesser degree they may be derived from hemorrhages. It is possible that in some cases a dermatofibroma merely represents a

keloid type of hyperplasia following a minor insult such as an insect bite or a short-lived hair follicle inflammation.

**DERMATOFIBROSARCOMA PROTUBERANS.**—This is a true fibroblastic tumor of the skin, but, unlike fibrosarcoma of the subcutaneous tissue, it is of a very low grade of malignancy and does not metastasize, so that local removal is sufficient. It commences as small nodules which fuse into a plaque. In the course of time the plaque develops into a protruding or mushroom-shaped mass. The clinical picture is often more suggestive of malignancy than is the *microscopic appearance*, which may be of very low grade or practically benign. There are interlacing bands of elongated cells which may show mitoses, but collagen formation is abundant.

**KAPOSI'S MULTIPLE HEMORRHAGIC HEMANGIOSARCOMA.**—This is a very rare form of angiosarcoma of the skin, usually on the hands and feet. The disease is very much commoner in men than women, and usually in Italians and Jews. The lesions consist of many foci of capillary clusters in a stroma of malignant spindle-shaped cells. The course of the disease varies greatly. The vascular nodules may undergo involution and form atrophic pigmented scars, or lesions may develop in distant portions of the skin and in nearly every organ of the body. The tumor is highly radiosensitive in the early stage.

**XANTHOMATOSES.**—Tumor-like lesions may result from the deposition of lipids in the dermis. As similar lesions occur in other connective tissues, the subject is discussed in connection with tumors of these tissues on page 249.

**GLOMANGIOMA. GLOMUS TUMOR.**—The word glomus means a conglomeration of minute arteries and veins. In the dermis of the extremities, particularly in the fingers and toes, there is an arteriovenous shunt by which the blood passes directly from the arteries into the veins without first passing through the capillaries. The channel along which the blood flows is lined by endothelium and surrounded by a mantle of large "epithelioid" or glomus cells; in addition there may be plain muscle fibers, while a rich plexus of non-medullated nerve fibers passes between the various cells. The epithelioid cells merge through a series of transitional forms with the typical spindle-shaped smooth muscle cells of the artery and vein. They appear to be derived from the pericytes of Zimmermann, specialized cells which are wrapped around the capillaries in all parts of the body and merge with the smooth muscle fibers (Murray and Stout). The entire mechanism constitutes a neuromyoarterial glomus, whose function appears to be to act as a kind of manometer controlling the circulation in the extremities and therefore the local temperature.

For the last one or two centuries the existence of "painful subcutaneous tubercles" in the extremities has been well recognized, but it was Masson who first in 1922 showed that these tumors arose from the glomus mechanism in the skin. Clinically these tumors are small, of slow growth, benign, confined to the extremities (common in the arm) and often situated under the finger nails, exquisitely tender, and characterized by paroxysms of burning pain during which the subungual lesions have a cyanotic appearance which is practically pathognomonic. Simple excision affords miraculous relief. A glomus tumor, however, may not be painful or even tender, depending probably on the amount of nerve fibers. *Microscopically* the tumor consists of a tangled mass of vessels surrounded by a fibrous capsule, and presenting the various elements (endothelial lining, glomus cells, plain muscle, and non-medullated nerve fibers) already described in the normal glomus (Fig. 560).

**GRANULOMA PYOGENICUM.**—This poorly named lesion is also known as *telangiectatic granuloma*, a much better term. It is a small, soft, red or bluish-red nodule, either pedunculated or sessile, which is highly vascular and bleeds readily. It often occurs at the site of an injury. *Microscopically* the nodule consists of

numerous newly formed capillaries and vascular spaces in a loose edematous stroma. (Fig. 561). At first the picture is one of granulation tissue with superadded infection.



FIG. 560.—Glomus tumor; glomus cells surrounding vascular channel.  $\times 225$ .

Later the appearance becomes almost purely angiomatous with little evidence of infection, so that the lesion may be taken for a hemangioma and finally for a dermatofibroma.

**LEIOMYOMA.**—This tumor appears as small firm nodules of the skin usually occurring in groups. They are often painful and tender on pressure. Microscopically they consist of smooth muscle fibers running in various directions. It seems probable that the tumors arise from the arrector pili muscles of the hair follicles.

**MYCOSIS FUNGOIDES.**—Various forms of lymphoblastoma such as leukemia, lymphosarcoma and Hodgkin's disease may involve the skin secondarily. The variety known as mycosis fungoides is a primary skin disease, although the internal organs may be affected later. It begins as a scaly eruption, with itching as a frequent symptom. After a period of months or years evidence of infiltration of the skin becomes apparent with the formation of elevated plaques. Finally the fungoid or tumor stage develops. The disease, like the other



FIG. 561.—Granuloma pyogenicum. The projecting lesion consists of vascular spaces in edematous stroma.  $\times 110$ .

lymphoblastomas, is invariably fatal. The *microscopic picture* in the infiltrative and fungoid stages is marked by a pleomorphism which may closely resemble that of Hodgkin's disease. The masses of cells in the dermis contain reticulum cells, histiocytes, polymorphonuclears, eosinophils, and giant cells. The last named are more indefinite in character than the Reed-Sternberg cells of Hodgkin's disease, having an appearance of cells clumped together, so that they may be called "pseudo-giant cells."

*Wood ticks* and the *venom of insect bites* may cause lesions of the skin easily mistaken microscopically for mycosis fungoides and Hodgkin's disease. To add to the confusion the epidermis often shows pseudo-epitheliomatous hyperplasia which may simulate early epidermoid carcinoma.

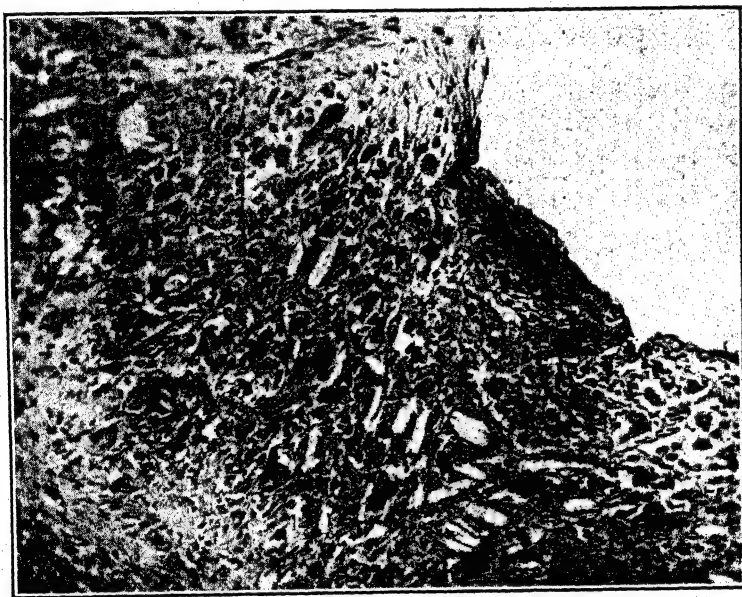


FIG. 562.—Ruptured epidermal cyst. Cholesterol clefts, squames, and giant-cell reaction.  
× 110.

### Cysts of the Skin

Dermal cysts may be dermoid, epidermal and sebaceous, and milium.

*Dermoid cysts* are easily recognized microscopically, because the wall is composed of skin with its appendages, *e. g.*, sebaceous glands, hair follicles and hair. They may be called trichosebaceous cysts. *Epidermal cysts* form the common and important variety. Most of the cysts called by the clinician sebaceous cysts are classified by the pathologist as epidermal cysts. True *sebaceous cysts*, commonly known as wens and occurring on the scalp, are the result of obstruction of the ducts of sebaceous glands and are lined by sebaceous cells. Epidermal cysts may arise *de novo* from the dermal appendages, they may result from squamous metaplasia of sebaceous cysts, or they may be traumatic owing to fragments of epidermis being displaced into the dermis as the result of trauma or operation (implantation cysts), or from the presence of a foreign body such as a splinter or thorn.

The *epidermal cyst* is lined by squamous epithelium, and the contents are greasy keratin, squames which accumulate as they cannot be shed, fat and cholesterol.

The cyst may rupture or leak into the tissues, where the contents excite a granulomatous reaction characterized by the presence of histiocytes, foreign body giant cells, cholesterol clefts, and the tell-tale squames (Fig. 562). At this stage the lining of the cyst may have disappeared, so that the true character of the lesion may not be recognized. There may be pronounced proliferation of the epithelium lining the dermal cysts with a simulation of carcinoma. Many of the cells may die but preserve their form and arrangement as is seen in an infarct of the kidney. This is known by the somewhat fanciful name of *mummifying epithelioma*. In other cases the cells become calcified, and the lesion is then a *calcifying epithelioma*. In rare cases there may be the development of a true carcinoma from the lining of a dermal cyst.

**MILIUM.**—This is a tiny white lesion of the *epidermis* no larger than a millet seed occurring in crops on the skin of the face, eyelids and genitalia. Each milium consists of a horny cyst developed in connection with the hair follicles, and may represent either a hyperkeratosis of the epithelium of the follicle or the retention products of sebaceous glands.

**COLLOID MILIUM.**—This condition is also known as colloid pseudomilium to distinguish it from the much more common true milium with which it has no relation, for it is a lesion of the *dermis*, not the epidermis. It takes the form of groups of lemon-yellow nodules the size of a millet seed or pin's head usually on the face and the backs of the hands of elderly persons. It represents a degeneration of the collagen and elastic tissue of the dermis. *Microscopically* the lesions are sharply defined hyaline or colloid masses in the dermal papillæ suggesting deposits of amyloid, which stain intensely blue with thionine, although remaining unstained with ordinary connective tissue stains. It seems probable, although not certain, that the material is a mixture of collacin and elacin, collacin being a degeneration product of collagen, as elacin is a similar product of the elastin of which elastic fibers are composed.

## SKIN MANIFESTATIONS OF INTERNAL DISEASES

The skin is a mirror of the health of the body. In this mirror may be reflected a wide variety of internal disorders. The skin has indeed been described as a mast from which signals of distress are flown. The subject is so vast that it would be absurd to attempt to do more than merely to allude to it here. Details can be found in Wiener's book.

Disorders of the endocrine glands may manifest themselves in the skin. Examples are the pigmentation of Addison's disease, the cutaneous and subcutaneous infiltration of myxedema, the hypertrichosis of adrenal cortical tumors, and the striæ of Cushing's disease. The pigmentation of hemochromatosis and jaundice becomes visible in the skin. Pregnancy is also associated with skin pigmentation and increased secretion of the sebaceous glands. In the lymphoblastomas such as lymphatic leukemia and Hodgkin's disease there may be infiltrations in the skin. Metabolic disorders such as diabetes and the lipidoses may be associated with xanthomatous skin lesions. The rash of the acute infectious fevers is often the most characteristic feature of these infections. The dermatological manifestations of the chronic granulomata such as syphilis and leprosy may be pathognomonic. Erythema induratum and crops of fleabitten petechiæ point to tuberculosis and subacute bacterial endocarditis respectively. Skin rashes, characteristic or otherwise, may be the result of drug intoxication. And so on, and so on.

All of which proves, if proof were needed, that the skin is indeed one of the most remarkable and important structures in the entire body.

## ADDITIONAL READING

- Ball-cell Carcinoma.** WALLACE AND HALPERT: Arch. Path., 1950, 50, 199.
- General References.** COWDRY: A Textbook of Histology, Philadelphia, 1950. LIVER: Histopathology of the Skin, Philadelphia, 1949. MACKENNA: Modern Trends in Dermatology, London, 1948. MCCARTHY: Histopathology of Skin Diseases, St. Louis, 1931. ORMSBY AND MONTGOMERY: Diseases of the Skin, Philadelphia, 1948. WIENER: Skin Manifestations of Internal Disorders, St. Louis, 1947.
- Dermatofibroma.** STECKER AND ROBINSON: Arch. Dermat. and Syph., 1941, 43, 498.
- Nevus and Melanoma.** ALLEN: Cancer, 1949, 2, 28. ALLEN AND SPITZ: Cancer, 1953, 6, 1. MASSON: Cancer, 1951, 4, 9.
- Scleroderma.** BEERMAN: Am. J. Med. Sci., 1948, 216, 458. SWARM AND GERMUTH: Am. J. Path., 1953, 29, 577.
- Sclerosing Hemangioma.** GROSS AND WOLBACK: Am. J. Path., 1943, 19, 533.
- Spontaneous-healing Squamous-cell Carcinoma.** CURRIE AND SMITH: J. Path. and Bact., 1952, 64, 827.
- Sweat Gland Tumors.** GATES, WARREN AND WARVI: Am. J. Path., 1943, 19, 591.
- Tumors of the Skin.** ELLER AND ELLER: Philadelphia, 1951.
- Verruca Vulgaris.** BUNTING, *et al.*: Am. J. Path., 1952, 28, 985.

## DENTAL PATHOLOGY

ALTHOUGH the care of the teeth belongs to the dental profession, the well-educated doctor should know at least something of the principal diseases of these structures, notably caries, periapical abscess, and pyorrhea alveolaris. A mere outline of these conditions is all that is attempted in the following pages.

**Anatomical Considerations.**—The teeth are homologous to the dermal scales of certain fish, and to such appendages of the mammalian skin as the hair and nails. A hair is a horny structure composed of epithelial cells resting on a papilla of connective tissue containing blood vessels and nerves. A tooth is a calcified structure formed by epithelial cells resting on a papilla of connective tissue; the outer part of this dental papilla becomes calcified to form the dentine, the inner part remaining as the dental pulp supplied with vessels and nerves.

A tooth is composed of four structures: (1) enamel, (2) dentine, (3) pulp (the formative tissue of the dentine), and (4) cementum. The *enamel* is the hardest of animal tissues, but it is brittle and easily fractured. The *dentine* forms the main bulk of the tooth; it is strong and elastic, therefore not readily broken. Such a specialized tooth as the elephant's tusk consists of dentine without any covering of enamel, as it is designed for digging and fighting, functions for which toughness is needed and brittleness is undesirable. The dentine is traversed by great numbers of fine channels known as the dentinal tubules which pass from the pulp outward to the inner surface of the enamel and cementum. As the dentine is formed from the dental connective tissue papilla it is mesodermal in origin. The *pulp* represents the remains of the formative organ of the dentine. The outer layer next the dentine contains specialized tall columnar connective cells, the odontoblasts, with long cytoplasmic fibrils which extend into the dentinal tubules; these are the only columnar connective-tissue cells in the body. In addition to the odontoblasts, the pulp contains numerous ordinary connective-tissue cells and abundant blood vessels, lymphatics, and nerves. The nerves end around the odontoblasts, but do not penetrate into the dentine, so that the odontoblasts form a connecting link between the sensitive dentine and the nerves. The nerves of the pulp respond in only one way when the dentine is stimulated by touch, heat or cold, and that is by pain. It is evident from what has been said that the constitution of the pulp enables that structure to develop a marked inflammatory reaction against bacterial infection, whereas no such reaction is possible in the avascular and acellular dentine and enamel. The *cementum*, which closely resembles bone histologically, covers the dentine in the root portion of the

tooth, and meets the enamel at the gingival line. It furnishes an attachment for the strong connective tissue fibers which fasten the root of the tooth to the bone of the alveolus. The *peridental membrane* or *pericementum*, which may be regarded as the periosteum of the tooth, is the fibrous connection between the bone and the cementum of the root. It is abundantly supplied with nerves which are responsible for the sensation felt when the tooth is touched. Atrophy of this membrane is followed by loosening of the tooth in its socket. Its normal functions may be summarized as nutrition, retention, and cushioning.

## CARIOES

Caries or dental decay is the most prevalent of all the diseases of the teeth. It has existed from prehistoric and early historic times. It is found in the teeth of Egyptian mummies. It is world-wide in its distribution, but certain races are remarkably exempt, *e. g.*, African natives and Eskimos. When these peoples adopt civilized customs, however, they tend to develop caries. The teeth are the hardest structures in the body, yet, under modern living conditions, the most perishable. The etiology of caries is a singularly complex subject involving a large number of factors both local and constitutional, a consideration of which will be postponed until the process itself has been described. Caries is primarily a disease of childhood, adolescents and young adults. The greatest susceptibility is at the period of the eruption of the teeth, the maximum incidence being in the interval of transition from the deciduous to the permanent teeth. The disease is commonest in the molars, then the upper incisors, then the bicusps; the lower incisors and canines are rarely affected.

**LESIONS.**—Dental caries is a unique process, unlike any other in human pathology. It must not be confused with caries of bone, which is an inflammatory reaction to infection, for we have already seen that neither the enamel nor the dentine contains the vessels and connective-tissue cells without which an inflammatory reaction is not possible. Caries may take either of two forms. The first, commonest between the ages of ten and sixteen, involves pits and fissures on the surface of the tooth, there is a very small point of entrance, and the progress is very rapid. The second, which occurs in adults, involves the smooth surface of the tooth, the point of entrance is large, and the progress of the disease is correspondingly slow.

The tissues affected by caries are the enamel, the dentine, and the cementum, with secondary infection of the pulp. The enamel consists almost wholly of inorganic material (salts), whereas the dentine consists of 30 per cent organic matter (collagen and elastin). The pathogenesis of cavity formation in these two structures will differ accordingly. The mineral salts of the enamel are soluble in acids, and it is by acids that they are dissolved in caries. These acids are produced from the carbohydrates of the food by acid-forming bacteria, and the opportunity for the acids to act is afforded by the presence of fissures or defects on the occlusal surface (Fig. 563). In other cases the process commences on the lateral surface at the point of contact of two contiguous teeth, both of the teeth being commonly affected. The acid (lactic, malic, formic, acetic) dissolves



the cement substance of the enamel at the bottom of the fissure, and a localized area of disintegration is produced which is wedge-shaped, with the apex at the surface and the base toward the enamel-dentine junction. When the process reaches the dentine it proceeds more rapidly and more widely, spreading laterally along the line of junction owing to the branching

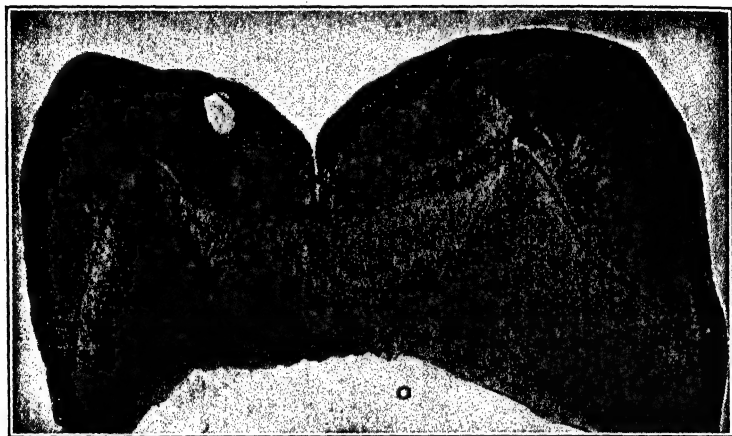


FIG. 563.—Deep fissure in enamel of occlusal surface. (Noyes.)

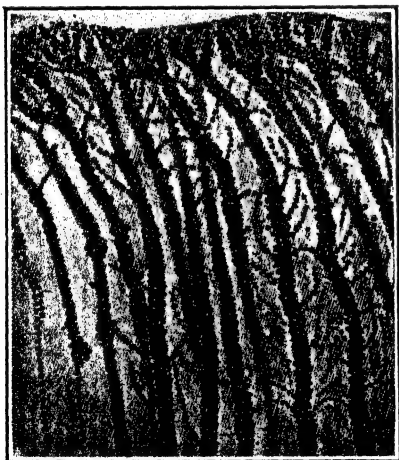


FIG. 564.—A drawing showing the microorganisms of caries growing through the dentinal tubules. (G. V. Black.)

of the dentinal tubules, and deeply into the dentine along the line of these tubules. The inorganic matter is here also dissolved, and again the area of disintegration is wedge-shaped, but this time with the base at the enamel-dentine junction and the apex toward the pulp. The bacteria spread readily along the dentinal tubules, so that the pulp is always potentially infected in every case in which the dentine is involved. (Fig. 564.) The organic matrix of the dentine is digested by proteolytic ferments of bacteria, which are either the original invaders or organisms of another group representing a secondary infection. As a result of the combined process a large area

of dentine may be destroyed with the formation of a cavity of considerable size, although the original lesion in the enamel may still be quite small. Eventually the remainder of the enamel may cave in, resulting in a sudden marked enlargement of the cavity. The process is a steadily

progressive one, as neither the enamel nor the dentine is capable of resistance or repair, although a formation of "secondary dentine" may be laid down between the dentine and the pulp, reducing the size of the pulp cavity; even this reaction is impossible in a devitalized tooth. The pain of caries is due to the inflammatory reaction which results from infection of the pulp.

**ETIOLOGY.**—The etiological agents may be divided into predisposing causes and exciting causes. The predisposing causes may be further subdivided into constitutional factors, *e. g.*, diet and heredity, and local factors, *e. g.*, anatomical, local hygiene, and the condition of the saliva. There is general agreement that the *exciting cause* is bacterial infection with acid-producing organisms, which break up the carbohydrates of the food débris with liberation of organic acids. These acids are said to be produced within five minutes of the end of a meal. Bunting believes that caries is a specific entity caused by infection with *Lactobacillus acidophilus*, and many workers are of this opinion, while others think that non-hemolytic streptococci and other organisms may act in a similar manner. The digestion of the organic matrix of the dentine may be brought about by the lactobacillus or perhaps by putrefactive strains of bacteria.

It is with regard to the *predisposing factors* that the greatest difference of opinion exists. The experimental work of May Mellanby with vitamin D and Howe and Wolbach with vitamin A has shown that avitaminosis leads to defective formation of the developing teeth, but there is no general agreement that there is any necessary relation between this defective formation and the development of caries. It is hardly safe to say more than that diet, in some manner apparently not depending on deficiency of any one ingredient, plays some part in the production of caries. There can be no doubt that a well-balanced diet, especially one lacking in cereals which have an inhibitory influence on calcification of teeth, is the best preventative of caries. In the little island of Tristan da Cunha, isolated in the south Atlantic, there is a community of white people with less caries than anywhere else in the world, and on this island no cereals can be grown owing to an infestation with rodents. It is of interest to note that there is not a single tooth brush on the island. In concentration camps dental decay ceases, possibly because of the absence of sugar in the diet.

The incidence of caries is low if the fluorine content of the water of the district is high, because fluorine renders the tooth less soluble during its development and formation. The topical application of sodium fluoride in childhood and adolescence has been shown to prevent caries to some degree. A constitutional factor of undoubted importance is heredity. Some families are almost immune to caries, while in others every member shows the disease in advanced form.

*Local factors* are of equal or greater importance. Anatomical defects in the shape of occlusal fissures in the enamel give the bacteria the opportunity to work unmolested with no danger of the acids they produce being washed away by the saliva. Local hygiene plays a part. While it is not true that a clean tooth is necessarily a healthy one, it stands to reason that continued removal of food débris will tend to prevent the establishment of the conditions favorable to the development of caries. The saliva is a local factor which may

be of great importance. In some mouths lactobacilli fail to flourish even when repeatedly introduced. This may depend on the pH of the saliva, or on other salivary factors so far undetermined. When caries begins on a smooth enamel surface it is due to the formation of a "bacterial plaque," a colony of bacteria which becomes attached to the surface as the result of some property of the saliva. The acids formed under this plaque are prevented from diffusing, and act locally on the enamel. Thus immunity to caries may be due to faultless enamel, or to the fact that the environmental conditions are inimical to the growth of saprophytes in spite of the presence of deep fissures in the enamel. From the above brief review it is evident that we can agree with the statement that "the complete story of the causation of dental caries cannot yet be written." (Appleton).

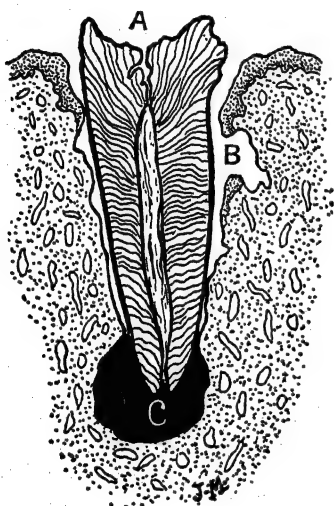


FIG. 565.—Dental disease. A, Caries affecting crown of tooth and penetrating down to the pulp. B, Pyorrhea: shrinking of bone and gum away from tooth. C, Root abscess.

### PERIAPICAL TISSUE INFECTION

We have already seen that when the integrity of the enamel is destroyed, infection readily passes along the dentinal tubules to reach the pulp. The result may vary from a mild pulpitis to severe suppuration, necrosis and gangrene of the pulp. The infection tends to extend through the apical foramen which admits the vessels and nerves, and may set up an acute periodontitis or a chronic apical periodontitis (dental granuloma).

**Acute Apical Periodontitis.**—This is likely to take the form of an abscess at the root of the tooth. The abscess may remain circumscribed as a *root abscess* (Fig. 565) or the suppuration may spread into the surrounding bone (osteomyelitis).

with the formation of an *alveolar abscess*. Such an abscess tends to discharge into the mouth either on the lingual or the labial side of the alveolar process. When the abscess is in the mandible, it may discharge on the skin surface. The regional submaxillary lymph nodes are swollen and tender.

**Granuloma.**—A *dental granuloma* or chronic apical periodontitis is a condition characterized by the formation of a mass of chronic inflammatory tissue around the apex of a tooth (Fig. 566). It therefore contains polymorphonuclear leucocytes, lymphocytes, plasma cells, mononuclear phagocytes, and fibroblasts in varying proportion, and is surrounded by a connective tissue capsule which blends with the healthy periodontal membrane, thus uniting the "growth" to the tooth. More distinctive is the presence

of masses of squamous epithelium, probably derived from the "paradental epithelial débris" of Malassez (Fig. 567). These are cell clusters found almost constantly in the periodontal membrane, and represent the remains of the enamel organ which extends as an epithelial sheath around the root



FIG. 566.—Two examples of dental granuloma. (Hill, Oral Pathology.)



FIG. 567.—Dental granuloma showing proliferation of its epithelial content. (Hill, Oral Pathology.)

(sheath of Hertwig) before the eruption of the tooth. The epithelial masses may proliferate as the result of the chronic irritation, and finally undergo cystic degeneration to form dental or radicular cysts. (Fig. 568.) The granuloma seldom if ever undergoes spontaneous resolution. The fibrous capsule and proliferated epithelium must be eradicated as well as the tooth extracted.

**Rarefying Osteitis.**—If the virulence of the infection and the acuteness of the reaction is less than in alveolar abscess but greater than in granuloma the result may be the condition known as rarefying osteitis. The inflammatory exudate at the apex of the tooth is not limited by a fibrous membrane, so that it infiltrates the adjoining bone. Thrombosis of the small nutrient vessels results in ischemic necrosis of bone and the formation of small sequestra with a foreign body giant-cell reaction. If the exudate extends to the surface, it forms the subacute swelling known as a gumboil. In the upper jaw the osteitis process may destroy the floor of the antrum and set up a maxillary sinusitis.

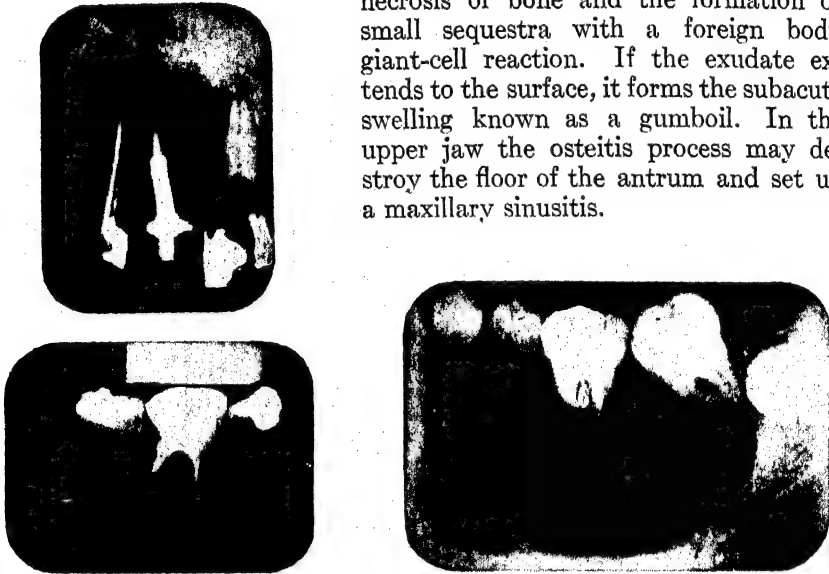


FIG. 568.—Cystic areas associated with periapical infection. (Hill, Oral Pathology.)

### PERIODONTAL DISEASE

The periodontium comprises the investing and supporting tissues which surround the tooth, namely, the periodontal membrane, the gingiva and the alveolar bone. Disease affecting these structures may be inflammatory, degenerative, or a combination of inflammation and degeneration. Gingivitis is a purely inflammatory lesion, whilst in periodonotosis the process is primarily a degeneration of the periodontium, with the later addition of a varying amount of infection.

**Gingivitis.**—The gingiva is the mucous membrane covering the alveolar processes and surrounding the neck of each tooth. It resembles the skin both in its histology and in its pathological reactions. Gingivitis is therefore analagous to dermatitis. It may be caused by trauma (food impaction between the teeth, excessive or improper use of the toothbrush, calcareous deposits on the teeth in contact with the gingival tissue), bacterial infection,

the excessive use of tobacco (pipe and cigarettes), and systemic disturbances such as general infections and the acute infective fevers. The *lesions* resemble those of dermatitis. The connective tissue papillæ are elongated and close to the surface so that their distended capillaries readily rupture. If the surface epithelium is eroded by trauma or ulceration, bleeding from the gums may be expected. In the severe cases there is a marked infiltration of the tunica propria and the epithelium with polymorphonuclears together with edema. In the chronic cases, due to continued infection or mechanical trauma, the gingiva becomes markedly thickened and elevated owing to hyperplasia of the epithelium and connective tissue so that it bulges between and around the teeth. Hyperplastic gingivitis may be associated with hyperplasia of adenoid tissue and habitual mouth breathing. The continued administration of dilantin may lead to marked gingival hyperplasia for reasons at present unknown.



FIG. 569.—Deep periodontal pockets on mesial of first molar and second bicuspid upper, due to traumatic occlusion of lower second molar. (Gabel, American Textbook of Operative Dentistry.)

The Achilles heel of the oral mucosa is the gingival sulcus, the shallow groove around the tooth bounded on one side by the tooth and on the other by the squamous epithelium of the gingiva. It is here that the soft tissues meet the tooth, and it is here, if the epithelium is damaged, that infection can reach the deeper periodontal tissue along the lymphatics of the periodontal membrane. Reference to the gingival sulcus brings us to the subject of periodontosis.

**Periodontosis: Pyorrhea Alveolaris.**—This very common condition is usually referred to as pyorrhea alveolaris, but pyorrhea signifies a flow of pus and most periodontal lesions have no visible purulent discharge. For this reason there is a tendency to discard the term pyorrhea in favor of such names as periodontal infection (exclusive of apical infection) and periodontosis. The advantage of the latter is that it indicates that inflam-

mation is not necessarily a dominant feature. Pyorrhea, however, is so convenient and familiar a term that it seems advisable not to jettison it completely. The condition is entirely unrelated to caries. Caries is a disease of the young; pyorrhea is more common after the age of thirty-five. In Tristan da Cunha, where caries is almost nonexistent, pyorrhea is quite prevalent. Caries is a disease of the teeth; periodontitis, as the name implies, is a disease of the surroundings of the teeth.

The primary lesion is an atrophy of the alveolar margin and the periodontal membrane (pericementum), as a result of which a gingival crevice is formed by separation of the oral from the enamel epithelium (Fig. 569). As long ago as 1771 that great student of disease, John Hunter, made the observation that marginal alveolar atrophy is the first lesion in pyorrhea. This crevice increases in depth and becomes lined by a downgrowth of oral epithelium. When the process of rarefaction and absorption extends sufficiently far, the tooth becomes loose and finally is lost. The condition is therefore in no sense a disease of the tooth. The x-ray picture is neither characteristic nor reliable. As soon as the tooth falls out or is extracted recovery occurs, but spontaneous recovery is impossible as long as the tooth remains in the jaw, for there is constant reinfection of the gingival space together with calcareous deposits on the root. The deep gingival crevice may be compared with the fissure on the occlusal surface of the tooth which forms the common starting point of caries. The food lodges in this crevice, infection occurs, and the result is a chronic suppuration of the periodontal membrane and the gum margins with accompanying discharge of pus. The gums are swollen, spongy, soft, and bleed easily; they may be dark red or pale. As the result of the suppuration the epithelium lining the crevice undergoes necrosis, and the bacteria invade the surrounding tissue. As a rule, however, the patient with pyorrhea appears to be in perfect health. The earliest *microscopic change* is a round-celled infiltration of the connective tissue at the apex of the gum margin. This infiltration spreads along the lymphatics under the epithelium lining the gingival trough and down the periodontal membrane. Fish is of the opinion that this chronic lymphangitis is responsible for the sequence of events, the chronic irritation causing the cementum to be absorbed and the epithelium to be stimulated to grow down and become attached to the healthy cementum.

The etiology of periodontitis has been the cause of much dispute, and, as in the case of caries, the factors to be considered are both constitutional and local. It appears probable that *constitutional causes* play a part in the alveolar atrophy which is the *fons et origo* of the condition. There is an osteoporosis and rarefaction which may be compared with that of osteitis fibrosa (Fig. 570). Box describes a rarefying pericementitis fibrosa, which allows a falling away of the gums from the tooth and the creation of a pocket. As in osteitis fibrosa and Paget's disease of bone there appears to be a disturbance in the balance of bone apposition and resorption. Many cases show an increase in the blood calcium. The blood phosphate is often low. It appears probable from experimental work on animals that the most important predisposing cause is a fault of nutrition, possibly connected with avitaminosis and disturbance of the acid-base balance of

the blood. There is no consensus of opinion as to whether any particular vitamin is at fault, but in the dog it has been found that vitamin A deficiency causes absorption of the alveolar process. The prevalence of pyorrhea in Tristan da Cunha may be related to the one-sided character of the diet. In support of the constitutional basis of the disease it may be noted that there is a close and frequent relationship between pyorrhea and diabetes mellitus.

The *local factors* take the form of local irritation and trauma, and may be regarded as exciting causes. The trauma caused by faulty occlusion of opposing teeth, loss of contact between the teeth, faulty fillings, and the formation of calcareous deposits, may, in the opinion of dental authorities, cause that recession of the bone from the tooth which is the essence of periodontal infection. The bacteriology is not constant. Non-hemolytic streptococci are most commonly found in the pus pockets and invade the gum. Spirochetes and fusiform bacilli are remarkably constant, but they are found in the presence of any decomposing organic material. *Entamoeba gingivalis* is frequently present, but appears to be quite nonpathogenic. Although infection is secondary and not primary, it is to the infection that any systemic results are due.



FIG. 570.—Rarification of bone in periodontosis. (Hill, Oral Pathology.)

## EXTENSION OF ODONTOGENIC INFECTION

Infection from a neglected periapical abscess may spread to surrounding structures and there cause serious damage. Three complications which deserve notice are osteomyelitis, deep neck infections, and maxillary sinusitis.

**Osteomyelitis.**—Inflammation of the jaws may be due to infection from a root canal, along the periodontal structures, or from the socket of an extracted tooth. This complication has largely disappeared owing to the use of antibiotics. A serious form of the disease is that which follows radiation therapy of intra-oral cancer. In the jaws the sequestrum is rarely entirely surrounded by new bone (involucrum), which forms only beneath it and at the sides. As a result, when the sequestrum becomes separated it is extruded on the surface and healing occurs with remarkable rapidity.

**Deep Neck Infections.**—Any oral infection may spread into the face or down into the neck. It may take the form of localized abscess or a spreading cellulitis. An *abscess* caused as a rule by staphylococci, is likely to arise from a periapical abscess, occasionally from an osteomyelitis. It will open either on the oral mucosa or on the skin. *Cellulitis*, called a phleg-



mon when severe, is a spreading inflammation of the connective tissue of the face and neck caused by fibrinolytic streptococci. The starting point is usually the lower jaw, but the infraorbital region may be involved from a maxillary tooth. It is through the loose connective tissue that the streptococci make their way most readily, and this is most abundant in the carotid sheath and in the lateral pharyngeal, submaxillary, sublingual and retro-pharyngeal spaces. These spaces are formed by the deep cervical fascia and its extensions. It is this fascia which governs the spread of infections in the neck. It ensheaths all the neck muscles and thus protects them. The fascial space superficial to the myohyoid muscle is large and extends across the neck to the other side, whereas the space deep to that muscle is much smaller and does not cross to the other side. Ludwig's angina is a rare form of severe phlegmon which involves the whole neck. Although usually a complication of one of the streptococcal fevers, it may occasionally arise from a mandibular molar tooth infection.

**Maxillary Sinusitis.**—Infection of the maxillary sinus or antrum usually comes from the nose, but in 10 per cent or more of cases it is said to be of dental origin. The roots of the first molar and second premolar and usually those of the second molar are immediately under the floor of the antrum, so that it is not remarkable that a periapical abscess of these teeth should occasionally discharge into the cavity and set up a sinusitis, either acute or chronic.

### FOCAL INFECTION

The term focal infection as commonly used does not indicate merely a focus of infection but signifies the setting up of secondary infection at a distance from the original lesions. With such a focus there are the following theoretical possibilities: (1) The bacteria may pass into the lymphatics and cause lymphadenitis of the regional lymph nodes. (2) They may enter the blood stream, multiply there, and set up an acute or chronic septicemia. (3) They may not multiply in the blood, but may settle in some distant part and multiply there. This is what is usually known as focal infection. (4) They may remain localized, but their toxins may be absorbed and set up degenerative and fibrotic changes in distant organs.

There are three possible foci of infection in relation to the teeth: (1) chronic periapical infection (root abscess, dental granuloma), (2) infection of the dental pulp, and (3) pyorrhea alveolaris. Of these, by far the most important is the dental granuloma, because of its confined character which facilitates absorption of bacteria into the vessels.

The observations and conclusions of Fish and MacLean on the relation of oral streptococci to focal infection are remarkably interesting. They found that cultures from the roots of extracted teeth, irrespective of the condition of the tooth, always showed streptococci, although there was no microscopic evidence of inflammation in the periapical tissue. The conclusion they draw is that the germs gain entrance to the root during extraction. In chronic infection the streptococci are confined to a necrotic nidus surrounded by leucocytes or they may take refuge in the dental canals. Thus a position of stalemate is established: the leucocytes are killed if they go in and the streptococci are killed if they venture out.

The organisms do not live in the living dental and paradental tissues, but they irritate them with their toxins. Fish and MacLean made the remarkable observation that streptococci appear in the blood within five minutes of extracting teeth in pyorrhea, and even chewing hard candies has the same effect of pumping germs from the infected gums into the blood. The blood soon becomes sterile, sometimes in ten minutes.

Almost every conceivable lesion has at one time or another been attributed to foci of infection in connection with the teeth. The following list of diseases is less open to criticism than the lengthy lists often drawn up by the enthusiastic advocates of focal infection; rheumatoid arthritis, myositis, endocarditis, nephritis, iritis and iridocyclitis. The problem is usually attacked from the angle of the patient suffering, say, from arthritis, and, as might be expected, roentgen-ray examinations will often reveal the presence of a quiet periapical granuloma. It is even more instructive to investigate the matter primarily from the dental standpoint. More than one large survey of university students with dental granulomas revealed by roentgen rays has been made, and such a survey has always showed that the persons with dental foci of infection have no more arthritis or heart disease than do the normal controls.

The concept of focal infection due to dental disease is not a new one for, as already mentioned in connection with the etiology of rheumatoid arthritis, the King of Assyria was advised by his physician 2500 years ago to have his teeth extracted because of the pains he suffered in his head and limbs. Since the day in 1910 when Sir William Hunter of London in an address to the medical students of McGill University first popularized the idea that dental infection might be responsible for inflammatory lesions in distant structures such as the heart, joints and muscles, the views of the medical and dental professions have fluctuated widely and wildly in relation to the subject. At one time removal of pulpless teeth for arthritis and rheumatism was as popular as removal of the appendix for discomfort in the right iliac fossa and of the ovaries for chronic pain in the female pelvis. The pendulum has now swung in the opposite direction. At the present time generalizations are dangerous as well as foolish. It is certainly the case that the relationship of dental infection with rheumatic and rheumatoid lesions has been greatly exaggerated, and that pulpless teeth with poorly filled root canals and chronic periapical infection may be completely harmless. It is equally true that just as a tuberculous bronchial lymph node may infect a distant kidney or bone, so may periapical infection result in inflammatory lesions of joints and other structures, especially in persons with a tendency, familial or otherwise, to systemic streptococcal infections with resulting lesions. The difficulty is to judge the frequency of this occurrence and to decide whether removal of infected teeth is likely to benefit the distant lesions. It would seem that each case must be decided on its own merits rather than on doubtful generalizations.

### CYSTS OF THE JAWS

The true cysts of the jaws, which may be compared with cysts of the skin, arise from embryonal epithelial remnants. In the development of

the tooth the crown is formed from the enamel organ. Downward extensions of the epithelium of the enamel constitute the sheath of Hertwig from which the apex of the tooth is derived. The tooth erupts towards the surface not continuously but in a series of fits and starts. With each of these bursts of growth little clusters of cells from the sheath of Hertwig are carried upwards with the connective tissue of the periodontal membrane. These clusters persist throughout the life of the tooth as the "epithelial débris" of Melassez, from which originate the lining of the dental cysts as well as the epithelial tumors of the jaws.

Of the epithelial cysts of the jaws, two, the radicular and the follicular, are odontogenic, being derived from epithelium that has been connected with the development of the tooth, whilst the third, the anterior median cyst, is derived from other epithelial remnants.

**Radicular Cyst.**—These cysts, also called periodontal cysts, are the most frequent of any that occur in the mouth. They are generally associated with chronic apical infection and develop in relation to a dental granuloma. The continued irritation of the infection appears to stimulate the remaining nests of cells of Hertwig's sheath (epithelial débris) to proliferate and fuse with the granuloma forming what has been termed an epitheliated granuloma. The center of the mass becomes necrosed, then liquefied, and finally converted into a cyst lined by squamous epithelium. The contents may be fluid or semi-solid containing cellular débris with cholesterol clefts and foreign body giant cells. If the infection remains active, the epithelium is destroyed, the lesion is surrounded by a fibrous wall, and the cyst remains small. If, however, the infection dies down, the epithelial wall persists, the cyst continues to grow expansively, and displaces the surrounding structures.

**Follicular Cyst.**—This lesion, also known as a *dentigerous cyst*, occurs in young persons and arises from the follicle of the developing tooth. It is generally associated with an embedded tooth. The follicle consists of an inner epithelial lining and an outer connective tissue covering. If the follicle becomes detached from the crown, though adhering to the neck of the tooth, fluid collects between the crown and the follicle with the formation of a cyst and pressure atrophy of the alveolar bone. The cyst is similar in structure to the radicular variety, being lined by squamous epithelium with fluid or semi-solid contents, cholesterol clefts, and giant cells. As there is usually no inflammatory element, the cyst can continue to grow and may attain a very large size. If infection should occur, the epithelium is destroyed and the cyst remains small.

**Anterior Median Cyst.**—This lesion is not connected with a tooth and is therefore not an odontogenic cyst. It occurs in the midline of the maxilla, and may take one of two forms. The first is lined by squamous epithelium, the second by columnar ciliated epithelium. The squamous epithelium is derived from islands of cells which remain at the line of closure of the three parts of the developing palate, whilst the columnar ciliated epithelium is derived from the nasal part of the developing palatine duct. In both of these instances, therefore, the cysts arise from embryonal epithelial remnants.

## ODONTOGENIC TUMORS OF THE JAWS

Tumors of the jaws may be odontogenic or non-odontogenic. Odontogenic tumors arise from the tooth or from embryonic structures from which the tooth originates. Non-odontogenic tumors are tumors of bone such as fibroma, fibrosarcoma, osteogenic sarcoma, giant cell tumor, etc. All of these have been described elsewhere.

Odontogenic tumors may be divided somewhat arbitrarily into odontomas and ameloblastomas or adamantinomas. The odontomas are tumors obviously connected with the teeth, whereas the ameloblastoma is a tumor of the jaw originating from epithelial remnants of the enamel organ, but with no obvious connection with a tooth.

**Odontomas.**—These lesions hardly deserve to be classified as true neoplasms, but rather as overgrowths of enamel, dentine, cementum, or a combination of these. They seem to originate in a disturbance of the dental follicle during the development of the tooth. If this disturbance occurs early, the enamel forming the crown is affected, if late, the dentine and cementum are involved. An enameloma, cementoma and dentinoma are recognized. The *enameloma* is the result of disturbance of the enamel organ during development. If this occurs before the enamel has begun to calcify, the tumor may be composed entirely of epithelial cells and might be regarded as a rudimentary ameloblastoma. The lesion is usually a mass of enamel attached to the tooth. The *cementoma* is much the commonest of the odontomas. It consists of a mass of cementum attached to the root of the tooth. It is an osteoma of dental origin. The *dentinoma* is an overgrowth of the root, and is the rarest of the odontomas.

**Ameloblastoma. Adamantinoma.**—This tumor has already been described on page 271, but reference must be made to it here. It is a rare tumor which if untreated, may grow to an enormous size with extreme destruction of the jaw. It may be mainly solid or mainly cystic. The tumor is usually innocent, but there may be invasion and rarely metastases. The microscopic picture varies to a marked degree. When differentiation of the enamel organ is advanced there is an outer palisade layer of columnar cells, the ameloblasts, and a central core of "star cells" with large vacuoles and connecting cytoplasmic bridges (Fig. 159, page 272). In other cases the picture resembles that of a basal-cell carcinoma. The *origin* of the tumor is considered to be from offshoots of cells from the enamel organ. Others consider that, at least in the basal-cell type, the origin may be from the basal layer of the oral epithelium with which a continuity may be established.

## ADDITIONAL READING

- Caries.** AGNEW, *et al.*: J. Pediat., 1933, 2, 190. ENRIGHT, *et al.*: J. Dent. Research, 1932, 12, 759. ROSEBURY: Arch. Path., 1933, 15, 260.
- Focal Infection.** HADEN: Dental Infection and Systemic Disease, Philadelphia, 1928. FISH AND MACLEAN: Brit Dent. J., 1936, 61, 336.
- General References.** APPLETON: Bacterial Infection with Special Reference to Dental Practice, 4th ed., Philadelphia, 1950. BOYLE AND KRONFELD: Histopathology of the Teeth and Their Surrounding Structures, 3rd ed., Philadelphia, 1949. CAHN: Pathology of the Oral Cavity, Baltimore, 1941. HILL: A Textbook of Oral Pathology, 4th ed., Philadelphia, 1949. THOMA: Oral Pathology, St. Louis, 1944.
- Odontogenic Tumors.** THOMA AND GOLDMAN: Am. J. Path., 1946, 22, 433.

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